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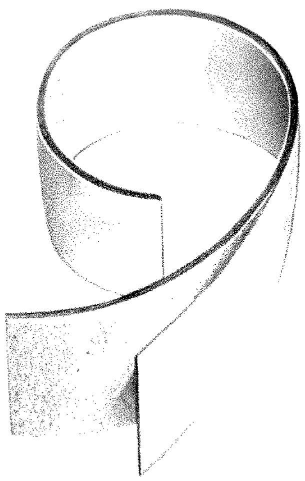

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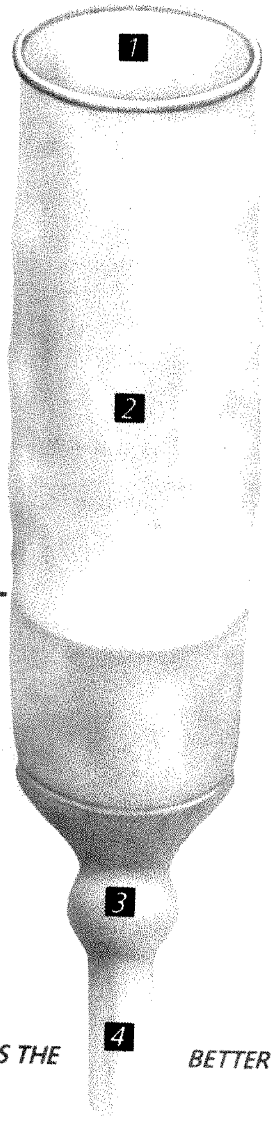

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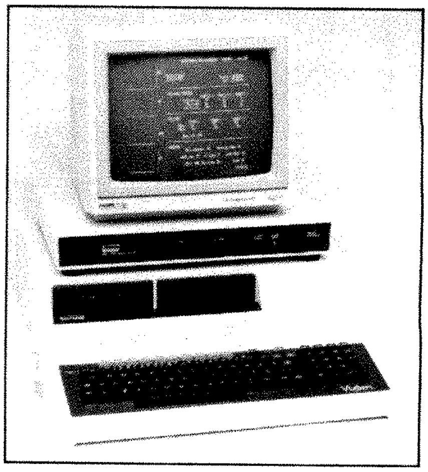

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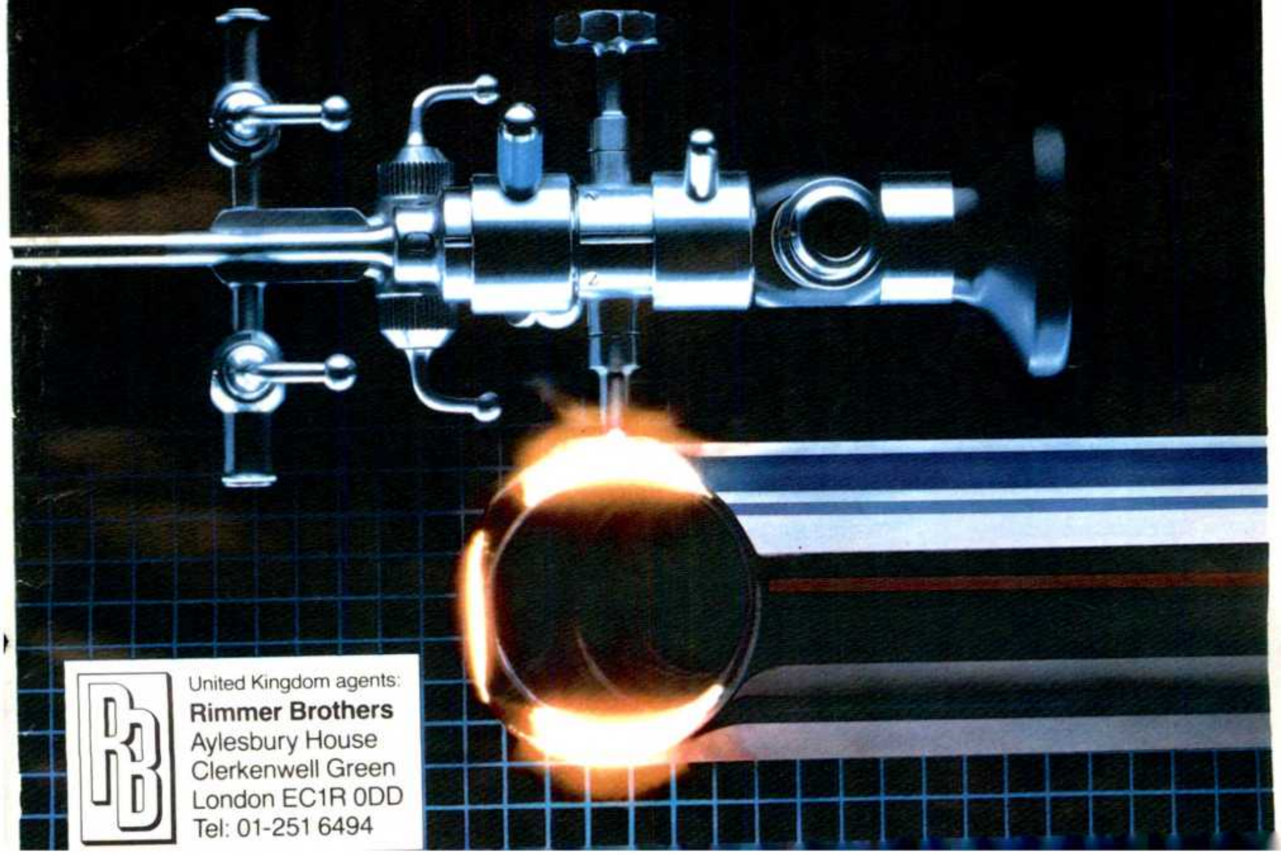

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Editorial

This issue of the British Journal of Urology marks a number of important changes in Journal policy. The first is that the Journal will now appear each month: this is in response to the steady increase in the number of manuscripts submitted and accepted for publication. Five years ago, when the time of acceptance to publication of an article lengthened to more than a year, the Editorial Board recommended an increase in the size of each issue. Now that the time to publication has again lengthened, the decision has been made for the Journal to appear monthly, in two volumes per annum.

The second change is the more diverse character of the contents: the basis of this Journal remains the refereed Original Article, but in response to a readership questionnaire we now have a regular Review article and short articles such as Authors' Follow-Up and Points of Technique. A very large number of Case Reports are submitted to the Journal and a monthly publication will allow for a greater proportion of these to be published each year.

The third change is the introduction of a correspondence column where the readers can comment upon or discuss journal contents. A bimonthly publication made it impractical to publish a letter together with the author's reply within a reasonable timescale; a monthly publication now makes this feasible and the Editorial Board look forward to an interesting response by our readers.

The fourth change has been to abandon the special issue of the Annual Meeting of the British Association of Urological Surgeons. In future, papers presented at the Annual Meeting and submitted ready for publication at the meeting will still continue to gain priority of publication—but whereas in the past these displaced the submitted papers, in future we expect that all manuscripts will be published more expeditiously, usually within 5 to 6 months. Thus most of the manuscripts relating to the Annual Meeting will continue to be published in the year of the meeting.

This Journal, as with similar publications, reflects the qualities and interests of subscribers. Requests for more (or less) articles for example on operative techniques, paediatric urology, urological research or urodynamics can only be met from submitted material and the Editorial Board believe that a monthly journal will now allow for readers' interests to be more readily met.

Geoffrey D. Chisholm

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REVIEW

The Current Management of Testicular Cancer

M. ELLIS and K. SIKORA

Department of Clinical Oncology, Royal Postgraduate Medical School, Hammersmith Hospital, London

The dramatic improvement in the management of testicular cancer provides the most heartening advance in oncology of the last decade. Over 85% of patients can expect to be cured of their disease and when disease is of low volume, the 5-year survival rate approaches 100% (Ellis and Sikora, 1985). These tumours are the commonest cancer in men in the 25 to 35-year age group and are steadily increasing in incidence (Nethersell *et al.*, 1984). The key to success has been the simultaneous development of effective combination chemotherapy with reliable non-invasive techniques to assess the extent of disease and its response to therapy.

As the numbers of patients successfully treated increases, it is clear that two major problems remain. The morbidity of intensive treatment is considerable. Unpleasant side effects are common and, of greater concern, a recent study reported a number of treatment-related deaths (Ellis and Sikora, 1986). Secondly, patients with bulky disease and high tumour markers, or those who fail to respond to standard management, have a persistently poor prognosis (Report from the MRC Working Party, 1985). With these problems in mind, this review will define the current roles of surgery, irradiation and chemotherapy in our attempts to achieve a balance between the highest probability of producing cure at the least cost to the patient in terms of toxicity.

Staging

Accurate staging, using tumour markers and CT scanning, is the first step in the management of testicular tumours once the diagnosis has been confirmed by orchiectomy. The Royal Marsden staging system, which is favoured in the UK, is based on CT assessment of the extent and bulk of metastatic disease (Peckham *et al.*, 1979) (Table 1). Tumour markers also help to establish the stage and may indicate metastatic disease in the absence of CT scan abnormalities (Stage I M). The level to which tumour markers are raised, as well as the radiological extent of disease, is important in determining prognosis. Bulky disease and high tumour markers (AFP > 500 ku/l and HCG > 1000 iu/l) identify a group of patients who have lower complete response (CR) rates with standard therapy and may be singled out for more aggressive treatment (Germa-Lluch *et al.*, 1980).

Table 1 Staging System for Testicular Tumours

I	Disease confined to testis
II	Infradiaphragmatic node involvement
	A: < 2 cm
	B: 2-5 cm
	C: > 5 cm
III	Supradiaphragmatic node involvement
IV	Extralymphatic disease
	L_1 lung metastasis < 3 in no.
	L_2 lung metastasis > 3 in no. < 2 cm
	L_3 lung metastasis > 3 in no. > 2 cm

Tumour markers

Serum assays of alphafetoprotein (AFP) and human chorionic gonadotrophin (HCG) are routinely used to stage testicular tumours, monitor response to treatment and detect relapse. One or both are raised in over 90% of patients with disseminated teratoma (Kohn and Raghavan, 1981).

AFP is a glycoprotein of molecular weight 63-70,0000 D. It is secreted by yolk sac elements

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within the tumour. The approximate half-life is 5 days. Since damaged liver can produce low levels of AFP, hepatotoxic chemotherapy or irradiation (Coppack *et al.*, 1983) can cause confusion. Monoclonal antibodies capable of discriminating between liver and tumour AFP may be useful in this context (Michael *et al.*, 1983).

HCG is synthesised by syncytiotrophoblastic cells. The alpha subunit is shared with FSH, LH and TSH. The C terminal 28 amino acids of the beta subunit are unique to HCG, however, and this provides the basis for a specific immunoassay (Vaitukaitis *et al.*, 1972). Although principally a marker of trophoblastic neoplasms, modest elevations of HCG (up to 100 iu/ml) are consistent with the diagnosis of seminoma, provided serial sectioning of the primary does not reveal trophoblastic differentiation typical of teratoma (Bosl *et al.*, 1981)

Several examples of tumours capable of producing only the beta subunit rather than the intact HCG molecule have recently been identified. HCG assays in this situation can be misleadingly normal, as only some are capable of detecting free beta subunit. The half-life of HCG is 24 h and the half-life of the beta subunit is 45 min.

The search for other markers, with the exception of placental alkaline phosphatase (PLAP) has been disappointing. PLAP is frequently elevated in seminoma and is related to disease bulk. Unfortunately, the high false negative and false positive results make it less reliable than AFP and HCG (Tucker *et al.*, 1985). It may be useful in the follow-up of a proportion of patients with seminoma.

It should be stressed that all patients should have tumour marker estimations before surgery is undertaken in order to detect occult teratoma in the primary and to aid follow-up, particularly in patients with normal post-orchiectomy markers. The complete resection of the primary tumour leads to a fall in marker levels inversely proportional to the serum half-life. A slower than predicted fall, a plateau or rising markers indicate residual disease. Response to treatment can be carefully monitored and a slow fall in marker levels after chemotherapy indicates resistance to treatment with the implication of poor prognosis. Regular marker estimations are a routine part of follow-up programmes and are a reliable lead to the early detection of relapse.

CT scanning

CT scanning is now an integral part of the assessment of testicular tumours (Husband and Grimer, 1985) and has replaced lymphangiography in most centres. Studies have shown that lymphangiography adds little to the diagnostic accuracy of CT assessment of the retroperitoneum, particularly with respect to a normal scan (Lien *et al.*, 1982). Surgical staging is now no longer performed routinely and so the CT scan must be performed with the utmost care in full knowledge of possible pitfalls.

The chief drawback of CT scanning is that nodal size is the only criterion for abnormality. Help in the interpretation of equivocally enlarged 10 to 15 mm nodes comes from a knowledge of the common patterns of metastasis. Borderline nodes should be regarded as more suspicious if they are on the same side of the aorta as the primary, since early contralateral spread is very uncommon (Dixon *et al.*, 1986). Particular note should be taken of areas where early nodal involvement is frequently seen, *e.g.* the anterior niche between the inferior vena cava and aorta for right-sided tumours and lateral and posterolateral to the aorta for left-sided lesions.

CT scanning has also proved invaluable in assessing lung metastases, since it is considerably more sensitive than conventional tomography (Munon *et al.*, 1978). Problems in interpretation have arisen recently because of bleomycin-induced lung fibrosis. Rescanning after a period of weeks is helpful in deciding on the aetiology of single nodules or areas of fibrosis (Rimmer *et al.*, 1986).

Surgical staging

Primary bilateral retroperitoneal lymphadenectomy is a standard way of staging patients with teratoma in the USA (Fraley and Narayan, 1985). It is undeniably the most sensitive way of detecting abdominal node metastasis. Whitmore (1979) estimated that non-invasive staging procedures miss 10 to 15% of retroperitoneal lymph node involvement. The Royal Marsden "follow-up only" experience of 109 patients (categorised Stage I by CT and tumour markers) supports this figure, as there were 11 retroperitoneal relapses. All of these patients were detected at an early stage and were successfully treated (Peckham, 1985).

The morbidity of lymphadenectomy is reasonably low, with the incidence of serious complications about 8%. Unfortunately, an almost universal consequence is permanent impotence, due to failure of ejaculation after damage to the sympathetic neural pathways during node dissection (Donohue and Rowland, 1981).

Protagonists of lymphadenectomy indicate its role as a curative procedure which, if successful, means the avoidance of chemotherapy. The figures indicate that if metastatic disease is clinically apparent at lymph node dissection, the patients will almost all relapse without subsequent chemotherapy (Javadpour and Ozols, 1982). Furthermore, "debulking" does not improve the chances of a successful outcome with subsequent chemotherapy (Blandy, 1985). If retroperitoneal disease is only discovered by histological examination of the resected nodes, only half will relapse if not given any further treatment (Oliver *et al.*, 1984). To put this in perspective, if the Royal Marsden's 109 patients managed by follow-up only were submitted to lymphadenectomy, perhaps six patients with retroperitoneal relapse could have avoided chemotherapy. This would be at the expense of exposing all 109 to the risks of major surgery and rendering the majority impotent. Thus the tide of opinion has turned against primary staging and is fast being replaced by non-invasive assessment, even by previous protagonists of this option in the USA.

The Management of Seminoma

Stage I. Adjuvant radiotherapy or follow-up?

Success in the management of metastatic seminoma predates that in teratoma by 40 years. This is due to a combination of its remarkable radiosensitivity and lower metastatic potential. Spread to the retroperitoneal lymph nodes usually occurs by orderly involvement of contiguous lymph node groups and early extralymphatic spread is uncommon. It has, therefore, been standard management to give adjuvant radiotherapy (3000 cGy in 15 fractions over 3 weeks) to the abdominal nodes and ipsilateral pelvic nodes in patients with Stage I disease, in the knowledge that the volume of any occult retroperitoneal metastasis is small and a relatively low dose of irradiation has a high chance of sterilising all deposits within the treatment field.

Although this approach is associated with a near 100% cure rate in Stage I disease, approximately 80% of patients receive irradiation needlessly, for perhaps only 20% have occult retroperitoneal node disease. The alternative is to adopt a follow-up only approach in a similar manner to that described for Stage I teratoma patients and irradiate only those who develop CT evidence of retroperitoneal node enlargement. This possibility has been explored in a number of centres in the UK. The Royal Marsden report 24 patients, followed up after orchiectomy for a mean of 13 months, with a zero relapse rate (only eight have been followed up for more than 1 year, however) (Peckham, 1985). The Institute of Urology report 10 of 11 patients observed having remained relapse-free for a median of 11 months' follow-up (Oliver *et al.*, 1984).

The principal objection to this policy is economic. In the absence of a reliable tumour marker (PLAP levels, so far, do not provide a basis to plan treatment without radiological relapse), a heavy strain is put on CT scanning units. Follow-up is expensive (Ellis *et al.*, 1984) and also has its psychological problems.

For the moment, we still recommend a policy of adjuvant irradiation, although there is a case for seminoma patients to be managed by follow-up only in clinical trials.

Stages IIa and IIb. Radiotherapy or chemotherapy?

The discovery that metastatic seminoma is as sensitive to cisplatin-based chemotherapy as teratoma, and possibly even more so, has led to a reconsideration of radiotherapy's hitherto pre-eminent position in treatment. All published series demonstrate that bulky abdominal, supradiaphragmatic and extralymphatic disease is inadequately treated by radiotherapy alone. The risk of relapse after irradiation is directly related to the size of the involved lymph nodes. In the 1982 Royal Marsden series, the relapse rate for Stage IIa was 9.4%, Stage IIb 18.2% and IIc 39.1% (Ball *et al.*, 1982).

In view of the low relapse rate, Stage IIa seminomas continue to be treated with radiotherapy. Most radiotherapists treat the abdomen and whole pelvis, in view of the occasional involvement of contralateral iliac nodes by retrograde tumour spread. Prophylactic mediastinal and supraclavicular fossa irradiation should not be carried out. The mediastinum is a rare site of relapse without extensive abdominal disease and the price paid is considerable myelosuppression. This will interfere with subsequent chemotherapy and result in a high incidence of second malignancies, particularly leukaemia (Einhorn, 1982).

It is difficult to be as dogmatic in recommending radiotherapy only for Stage IIb, although this remains the standard approach. In view of the encouraging single agent cisplatin and JM8 data in bulky disease (*q.v.*), chemotherapy seems a reasonable alternative. Without a clinical trial, it is not clear if the extra toxicity of chemotherapy justifies the reduced relapsed rate one would expect. For

Stage IIc disease, clearly the relapse rate with radiotherapy alone is unacceptable.

Stages IIc, III and IV. Chemotherapy with or without radiotherapy?

The optimal roles for radiotherapy, combination or single agent chemotherapy in the management of advanced seminoma are currently under review. Recently published work confirms that platinum-based chemotherapy is superior to radiotherapy alone. The use of these regimens achieved a 90% survival (median observation time 36 months) of 44 patients with advanced seminoma, treated at the Royal Marsden between 1978 and 1983 (Peckham *et al.*, 1985). Initially, patients were treated with cisplatin, vinblastine and bleomycin in line with Einhorn's earlier observations of the value of this combination. Myelosuppression, particularly in irradiated patients, was a problem now mitigated by replacing vinblastine with etoposide. This new combination, BEP (bleomycin, etoposide and platinum) has become standard management for advanced seminoma and teratoma alike (Peckham and Barrett, 1983). Evidence that we might be overtreating the majority of patients with seminoma with this combination comes from a series of 12 patients treated with single agent platinum. Ten of 12 achieved long-term complete remission (Oliver *et al.*, 1983). These data are complemented by five patients treated with the platinum analogue JM8 alone, with four of five achieving durable complete remissions.

As well as chemotherapy, patients have received radiotherapy to bulky disease, either after two courses or at the completion of chemotherapy. We do not know if this is necessary. One study showed clearly that the relapse rate after chemotherapy was not reduced by subsequent radiotherapy (Peckham *et al.*, 1985).

Without more clinical trial data it is impossible to recommend a standard treatment for advanced seminoma. BEP remains the safest course of action. After two courses, 3000 cGy is given to any bulk disease remaining, followed by a further two courses of BEP. Masses may remain after treatment, but surgery is not indicated as they gradually resolve.

The Treatment of Teratoma

Stage I. Surveillance

The observations made on the behaviour of seminoma, that explain its overall good prognosis, do not hold for teratoma. These tumours are less radiosensitive, have a high metastatic potential and early extralymphatic metastasis is common. Consequently, localised treatment to retroperitoneal disease is less likely to be successful. On this basis, systemic chemotherapy is now the standard management of extratesticular disease at any state of tumour progression.

The treatment options in Stage I testicular teratomas include adjuvant abdominal and pelvic radiotherapy, lymphadenectomy, adjuvant chemotherapy, or no treatment, with careful follow-up and chemotherapy in relapse (Oliver *et al.*, 1983). Radiotherapy, as adjuvant treatment to the abdominal and pelvic nodes, was standard management until recently and still has its protagonists (Hope-Stone, 1985). Certainly it would reduce the retroperitoneal relapse rate, which is 10% in those followed without initial treatment. It is unclear how effective it would be, however, and retroperitoneal relapse after radiotherapy is not uncommon. The disadvantage is that 90% of patients receive unnecessary irradiation. Some will subsequently develop extralymphatic or supradiaphragmatic relapse and may develop marrow toxicity when given chemotherapy. Furthermore, as the dose of radiotherapy is higher than for seminoma (with 4000 cGy in 20 fractions being standard), the attendant risks of enteritis, spinal cord irradiation and second tumour are greater. The current view is that adjuvant radiotherapy, like primary lymphadenectomy, should be abandoned and most oncologists are now converted to a policy of follow-up only. The occasional patient, who is unable or unwilling to attend the intensive follow-up programme necessary, may still warrant adjuvant radiotherapy to the nodes at risk.

The latest update on the largest surveillance series from the Royal Marsden of 109 patients reports a relapse rate of 27.5%. The risk of relapse was higher (46%) in those with MTU histology. The presence of vascular invasion in the primary is also a strong risk factor for relapse, with 25 of 29 patients with this histological feature relapsing in another recent series (Moriyama and Daley, 1985). This raises the possibility of using adjuvant chemotherapy in patients with MTU histology with vascular invasion. Certainly these patients warrant particularly close follow-up.

In summary, patients identified as Stage I by CT scans of the chest and abdomen, routine blood biochemistry and serum AFP and HCG, do not now receive any treatment beyond their orchiectomy. Transcrotal needle biopsy, scrotal orchiectomy or prior orchiopexy are not contraindications to sur-

Table 2 Combination Chemotherapy Response Data for Metastatic Teratoma

Year	*Regimen*	*Patient no.*	*CR no.*	*% CR*
1960	ACT-MTX-CLB	23	3	11
1966	ACT-MTX-CLB	90	11	12
1975	VBL-BLE	70	22	30
1977	CDP-VBL-BLE	50	35	74
1983	POMB-ACE	69	58	83
1983	BLE-ETO-CDP	36	30	84

Abbreviations

ACT	Actinomycin D
MTX	Methotrexate
CLB	Chlorambucil
VBL	Vinblastine
BLE	Bleomycin
CDP	Cis-diammine dichloroplatinum
POMB	Cisplatin, Vincristine, Methotrexate, Bleomycin
ACE	Actinomycin D, Cyclophosphamide, Etoposide
ETO	Etoposide

veillance. Patients attend the clinic monthly for 1 year, then 2-monthly for the second year and 3-monthly for the third year. CT scans are performed routinely at 3, 6 and 12 months, but may be repeated more frequently if suspicious. Chest X-rays, HCG and AFP are routine at each visit. With this approach, over 70% escape any further treatment, a major improvement in management.

Stage IIa–IV. Combination chemotherapy

The historical background of current chemotherapy has been well reviewed elsewhere (Bagshawe *et al.*, 1983). Table 2 summarises the uncontrolled patient series that reported the stepwise improvement in prognosis over the last 20 years. Our patients currently receive the BEP combination (Table 3). After four courses the patient is reassessed. If complete remission was obtained after two courses, no further chemotherapy is given. In all patients, two courses beyond complete remission are given. Our complete response rate is currently 87%.

Patients receiving the original PVB regimen have a complete response rate of 68%; the response in bulky disease is poorer, with less than 60% achieving complete remission (Einhorn and Donohue, 1977). A second advantage of BEP over PVB is its lower myelotoxicity. The use of PVB has been associated with a number of deaths from septicaemia.

Table 3 The BEP Combination Currently Used

Bleomycin	30 mg i.v. weekly
Etoposide (VP16)	120 mg/m² i.v. × 3 every 3 weeks
Cisplatin	30 mg/m² i.v. × 3 every 3 weeks

Attempts to reduce toxicity in small volume disease by avoiding bleomycin with its attendant cutaneous, lung and vascular problems have been unsuccessful, with seven of 16 evaluable patients failing to achieve complete response or showing evidence of disease progression. In patients with lung toxicity, vinblastine can be used instead of bleomycin (PEV). This combination produces similar responses to those seen with BEP in both small volume (BEP 92% CR, PEV 92% CR) and bulky disease (BEP 79% CR, PEV 75% CR), although the numbers treated in this way are small (Wilkinson, 1985). The Charing Cross group also report good results in bulky disease with combinations containing etoposide. They recommend a complicated regimen of vincristine, methotrexate, bleomycin and cisplatin (POMB), alternating with actinomycin D, cyclophosphamide and etoposide (ACE). Complete responses were obtained in 20 of 23 patients (87%) with Stage IIc abdominal disease, 20 of 24 (84%) with advanced lung disease and eight of 10 with both, if they had received at least two courses of POMB/ACE (Newlands *et al.*, 1983). It is likely that POMB/ACE is overtreating small volume disease. Whether it is the treatment of choice in bulky disease can be answered only by clinical trial. Other possibilities for improving the response rate in bulky poor prognosis disease include increasing the dose of platinum, the use of new platinum analogues (JM8) and reducing the interval between courses.

Brain metastasis is not infrequent and a number of cures have been observed. A combination of cranial irradiation and a methotrexate-containing combination such as POMB/ACE may be the treatment of choice. Methotrexate can penetrate the blood brain barrier reliably.

Post-chemotherapy surgery

As a result of the poor response rate of bulky metastatic disease to PVB, surgical resection of chemotherapy-resistant masses has been investigated. Despite the better reponse rates with combinations containing etoposide, post-chemotherapy resection of tumour masses is now standard treatment for residual bulky disease. In a series of 73 patients (Tait *et al.*, 1984), resected tissue was found to contain residual malignancy in 10 (23%), fibrosis and necrosis in 25 (34%) and differentiated (mature) teratoma in 32 (44%). As well as a therapeutic procedure, the operation has great value as a secondary staging procedure. Residual tumour is an indication for further chemotherapy, but indicates a poor prognosis, with less than half remaining disease-free following surgery.

Although raised pre-surgical markers indicate residual disease, there is no characteristic radiological feature that can differentiate between the histological findings of fibrosis, mature teratoma or malignant disease. Reports of sarcomas arising in these post-chemotherapy masses further reinforce the need for surgery (Ahlgren *et al*, 1984). It is recommended that full node dissection is carried out, rather than limiting the operation to clinically apparent disease. Small lymph node deposits are not infrequently found separate from the main mass of tumour.

Toxicity problems

The complications of intensive chemotherapy are considerable (Table 4) A recent detailed analysis of mortality in 460 patients with testicular cancer, treated in a regional hospital setting between 1980 and 1984, revealed 12 treatment-related deaths (Ellis and Sikora, 1986). Presumptive or proven septicaemia contributed to death in five patients, all of whom had widespread teratoma and were being treated with PVB. Two had received prior radiotherapy which increased the degree of myelosuppression. As previously discussed, radiotherapy should be avoided in teratoma for this reason. The incidence of septicaemia with the BEP combination is lower than with PVB, as etoposide is less myelosuppressive than vinblastine. No deaths from septicaemia were recorded with this combination. White counts of <2.5 contraindicate further chemotherapy at 3 weeks. There is no evidence that a delay to 4 weeks reduces the effectiveness of the BEP combination, at least in small volume disease.

Table 4 Complications of Chemotherapy

Haematological	*Neurological*
Anaemia	High tone deafness
Neutropenic sepsis	Encephalopathy
Thrombocytopenia	Peripheral neuropathy
Leukaemia	Cerebral bleeding
Respiratory	*Gastrointestinal*
Lung fibrosis	Nausea and vomiting
Adult respiratory distress syndrome	Diarrhoea
Pneumonitis	
Cutaneous	*Renal*
Epilation Allergy	Nephrotoxicity
Skin pigmentation Angio-oedema	
Desquamation	
Vascular	*Metabolic*
Raynaud's phenomenon	Hypomagnesaemia
	Hypokalaemia

The cause of death in two patients, who died suddenly on chemotherapy, was not apparent. Possible factors include electrolyte disturbances after continued vomiting at home, septicaemia, intracerebral haemorrhage or renal failure These deaths should be preventable and patients should not be sent home after a course of chemotherapy unless vomiting has ceased and electrolyte imbalance is unlikely. The general practitioner should be vigilant and a 24-h access to oncological advice should be readily available.

Renal failure contributed to the cause of death in three patients. In general, forced diuresis protects the kidneys from platinum nephrotoxicity, but it should be noted that hypokalaemia, induced by this, contributed to the cause of death in one patient. Regular estimation of GFR, if necessary, using a radioisotope technique, should be carried out between doses of platinum. Should severe renal failure develop, there should be no question about the need for dialysis. Unfortunately, cisplatin chemotherapy must be stopped and alternative regimens substituted. New platinum analogues such as JM8 (carboplatin) with less renal toxicity are now available and so the mortality and morbidity from renal failure and forced diuresis should be eliminated.

Two patients with widespread lung metastases developed acute respiratory distress soon after their first course of chemotherapy. This syndrome, probably triggered by tumour lysis, should be considered when patients with extensive lung disease are to be treated. A careful watch over respiratory function must be maintained and it may be justified to modify the initial doses of chemotherapeutic drugs to lessen the risk. Chronic lung fibrosis due to bleomycin is common and may lead to stopping bleomycin treatment. Respiratory function testing, although not routine, should be carried out immediately if the patient complains of dyspnoea.

In summary, the major complications of chemotherapy can often not be avoided, but their early recognition and correct management should lead to minimal treatment-related mortality in this highly responsive disease.

The management of testicular cancer represents one of the greatest achievements in clinical oncology of the last few years. As with other successfully treated tumours, such as Hodgkin's disease and the leukaemias, several factors are responsible. Clearly identifiable are the newer assessment and monitoring techniques, effective chemotherapy, better sup-

Table 5 Management Strategy for Testicular Cancer

Stage	*Seminoma*	*Teratoma*
I	3000 cGy para-aortic and ipsilateral pelvic nodes	Surveillance
IIa	3000 cGy para-aortic and bilateral pelvic nodes	BEP chemotherapy. Consider more aggressive regimens for poor prognostic groups
IIb	500 cGy boost to main disease	
IIc III IV	BEP chemotherapy 3000 cGy to site of residual tumour bulk if CR not achieved rapidly	

portive care and a greater understanding of the biology of the disease. Table 5 outlines a stage-by-stage management plan using our existing knowledge. A major problem facing the clinical investigator is the paucity of patients in any one centre, caused by the wide dispersion of oncology skills in community hospitals. The main question which now needs addressing is how far we can reduce the use of aggressive therapy and still maintain high cure rates. The accrual of patients with poor prognosis disease into trials of intensive treatment is also a priority. New assessment methods, immunohistology, new tumour markers, perhaps using oncogene products, may allow precise prediction of the eventual outcome with a given treatment regimen.

At a time when so little seems to be happening to improve the management of solid tumours, the dramatic success story of chemotherapy and surgery provides a model for the management of other cancers in the future.

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Modified Method of Diuresis Renography for the Assessment of Equivocal Pelviureteric Junction Obstruction

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Summary—Thirty-five hydronephrotic kidneys, in which diuresis renography showed either an equivocal (13) or non-obstructive (22) response pattern, were studied by a modified method in which intravenous frusemide was given 15 min before the start of the renogram so as to assess elimination during the period of maximum diuresis. Thirteen kidneys were identified as obstructed, including three in which the standard diuretic renogram appeared to exclude obstruction. These results indicate that the modified method increases the specificity of diuresis renography when used to assess patients with equivocal pelviureteric junction obstruction.

Diuresis renography is widely used for assessing upper urinary tract dilatation. It is usually performed by administering intravenous frusemide during the renogram if there is absent or slow elimination of tracer from the kidney at 15 to 20 min after the start of the test. If elimination remains impaired after the diuretic, obstruction is confirmed, but a resultant rapid fall in the level of tracer in the kidney is thought to exclude any mechanical restriction to the flow of urine (O'Reilly *et al.*, 1978; Koff *et al.*, 1979).

Although several studies have indicated the value of diuresis renography in idiopathic hydronephrosis (Lupton *et al.*, 1979; O'Reilly *et al.*, 1979, 1981; English *et al.*, 1982), it has also been suggested that the test has a significant false negative rate for obstruction in this condition (Hay *et al.*, 1984; Whitaker and Buxton-Thomas, 1984). It is known from pressure/flow studies that a very high flow rate is sometimes necessary for obstruction to be apparent at the pelviureteric junction (PUJ) (Johnston, 1969; Pfister, 1982), but in diuresis renography, although an increase in urine flow usually occurs within 3 min of intravenous frusemide, the peak effect of the diuretic is not reached until several minutes later (Cutler *et al.*, 1974). Hence it is conceivable in some kidneys that the initial increase in urine flow during diuresis renography could result in rapid and complete elimination of tracer from the renal pelvis before the diuresis has reached a level sufficient to show an obstructive effect.

To test this hypothesis, diuresis renography was modified in the present study by giving intravenous frusemide 15 min before the start of the renogram so that excretion could be assessed during maximum urine flow. This modified method was used for the further evaluation of cases of renal pelvic dilatation in which standard diuresis renography was either equivocal or indicated non-obstructive dilatation.

Patients and Methods

Thirty patients (age range 7-60 years) were included in the study and were investigated initially by intravenous urography (IVU) for the reasons shown in the Table. Twenty-four kidneys were considered normal. In 35 kidneys, including a single kidney in one patient, PUJ obstruction could not be excluded by the IVU and in these kidneys the re-

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Table Symptomatology

Presenting complaint	*Number of patients*
Loin pain	24
Urinary tract infection	2
Haematuria	2
Previous vesico-ureteric reflux	2

sults of standard diuresis renography were either equivocal (13 cases) or suggested non-obstructive dilatation (22 cases). Parenchymal function, as assessed by renography, was preserved in all cases. Diuresis renography using the modified technique was usually performed within four weeks of the first renogram.

The renographic studies were performed with the patient in the seated position using an intravenous injection of ^{123}I hippuran (0.2 MBq/kg) and a gamma camera-computer system. With standard diuresis renography, intravenous frusemide (0.5 mg/kg body weight) was injected between 15 and 20 min after the start of the renogram, whereas a similar dose of frusemide was given 15 min before the renogram in the modified test. All patients were encouraged to empty their bladders just before the radioisotope was injected. Oral fluids were not administered before the standard test if the patient was normally hydrated but 500 ml of water or fruit juice were given routinely 30 min before the modified diuretic renogram.

The results of both standard and modified diuresis renography were assessed qualitatively but an attempt was also made to compare the results quantitatively. Response patterns with standard diuresis renography were measured by the diuresis excretion index (DEI) (Fig. 1) (O'Reilly *et al.*, 1978). The modified test was quantified by an index of excretion (T½) representing the time from the peak of the renogram until the activity in the kidney had fallen to 50% of its maximum value (Fig. 2). In both tests the indices were derived from renogram curves in which the background component had been subtracted.

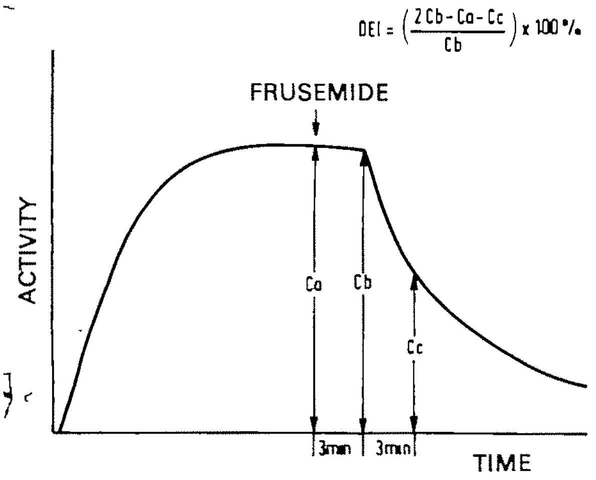

Fig. 1 Standard diuresis renography—diuresis excretion index (DEI).

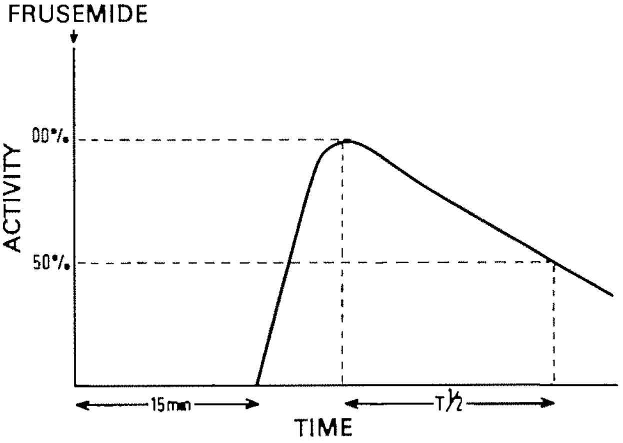

Fig. 2 Modified diuresis renography—index of excretion (T½)

Results

Excretion indices obtained with the two methods of

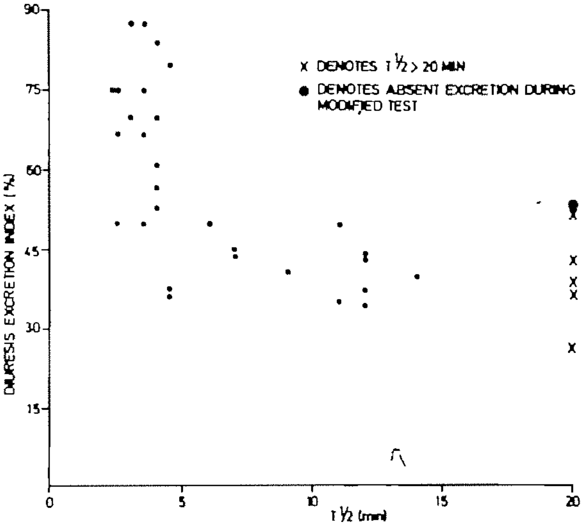

Fig. 3 Comparison of diuresis excretion and T½. DEI > 45% or T½ < 5 min denotes non-obstructive response. T½ > 10 min denotes obstructive response. Other values of indices correspond to equivocal responses.

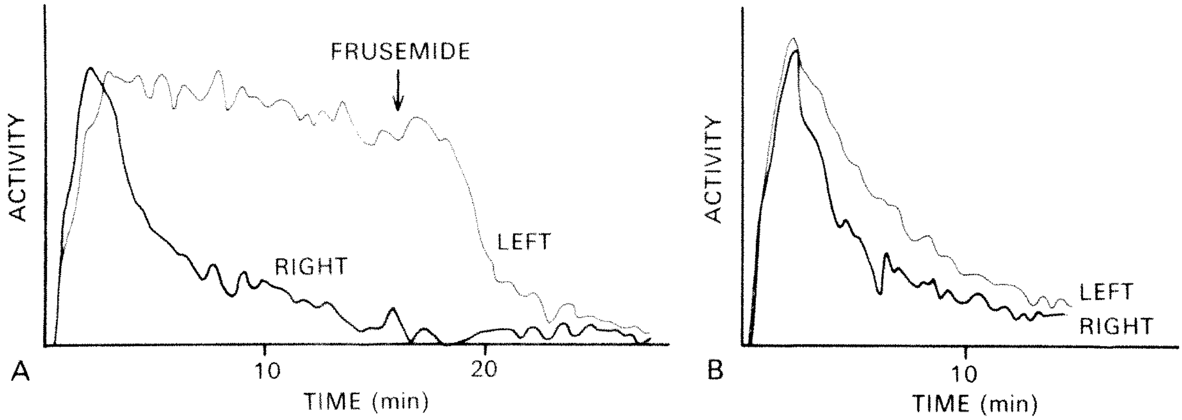

Fig. 4 Dilated left renal pelvis. Standard (A) and modified (B) diuretic renograms show non-obstructive patterns.

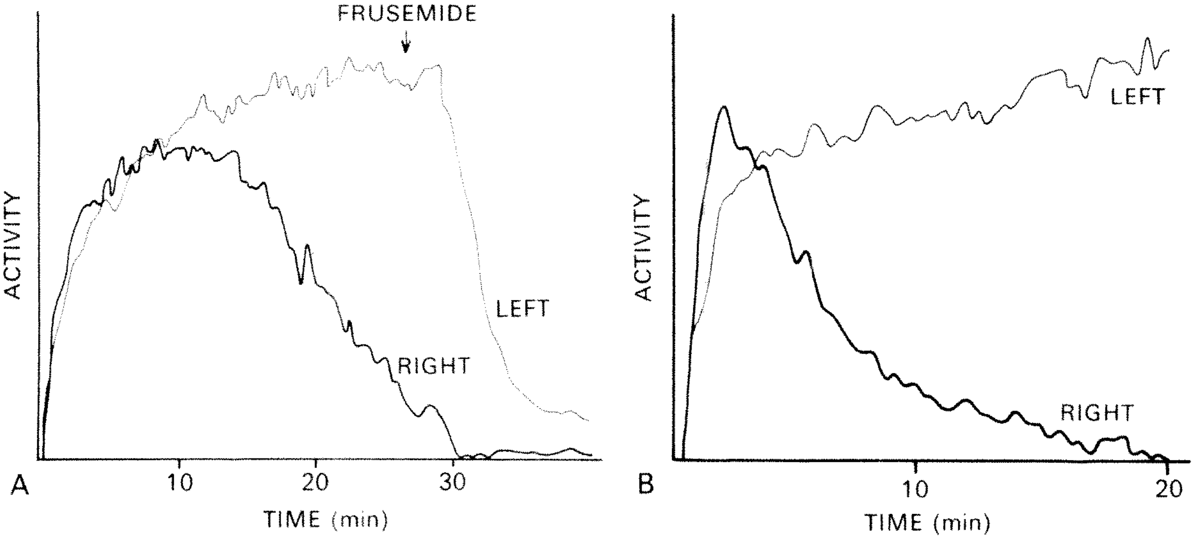

Fig. 5 (A) Obstruction to left kidney not apparent on standard diuretic renogram (DEI = 53.6). (B) Obstruction clearly demonstrated when intravenous frusemide administered 15 min before renogram.

diuresis renography were compared for the hydronephrotic kidneys (Fig. 3). Eighteen of these kidneys had T½ values less than 5 min, similar to values seen in the normal kidneys in this study (range 1-4 min) (Fig. 4). A further 13 kidneys (10 equivocally obstructed, three unobstructed on standard diuresis renography) had T½ values greater than 10 min, indicating obstruction to urine flow. This latter group included one kidney in which total obstruction was observed during modified diuresis renography despite an unobstructed standard test (Fig. 5) and another five kidneys in which elimination from the renal pelvis was very slow (T½ >20 min). Equivocal T½ values (range 5-10 min) were obtained in four kidneys.

Two patients underwent acute urography at the time of pain, which confirmed obstruction at the pelviureteric junction. In these patients the results of standard diuresis renography were equivocal in one case and showed a non-obstructive pattern in the other, but obstruction was correctly demonstrated by the modified test in both cases.

All patients experienced a profound diuresis throughout the period of the modified test. In six control patients, urine flow was calculated between 22 and 35 ml/min over a 20-min period from the start of the renogram.

Discussion

By definition, PUJ obstruction results in restriction of urine flow between the renal pelvis and ureter. In some kidneys, however, obstruction is apparent only during high urine flow rates. This is demonstrated clinically in patients with intermittent loin pain precipitated by a high fluid intake in whom standard IVU is normal but an obvious hydronephrosis is seen after a potent diuretic stimulus (Davies *et al.*, 1978). Johnston (1969) also showed experimentally that perfusing the renal pelvis at 10 ml/min induced complete obstruction in some hydronephrotic kidneys, whereas outflow matched inflow in the same kidneys when the perfusion rate was only 5 ml/min. Occasionally, perfusion rates as high as 15 ml/min may be necessary to demonstrate obstruction (Pfister, 1982).

The mechanism by which a high urine flow induces obstruction in idiopathic hydronephrosis remains uncertain. Although it is generally believed that the aetiology of PUJ obstruction involves a functional abnormality at the junction itself, previous observations have suggested mechanical factors as a possible cause in some kidneys (Stewart, 1947; Adams, 1951; Johnston, 1969). More recently, Hickinbotham (1983) reported good results in a prospective study of 15 patients undergoing lower polar vessel translocation (Hellstrom operation) combined with pelviureterolysis and concluded that lower polar vessels are a common cause of obstruction.

Although lower polar vessels are not evident in all cases of PUJ obstruction, it is interesting to speculate on whether they play a role in obstruction associated with a diuresis. In this context, the closed type of junction with a rounded renal pelvis could be important in that distension of the pelvis resulting from the high urine flow may be sufficient to allow compression of the first part of the ureter by the polar vessels. This effect could also be exaggerated in the upright posture in some patients (Hanley, 1959).

In the present study, obstruction at the PUJ was more clearly demonstrated by diuresis renography when intravenous frusemide was given 15 min before the renogram rather than in continuity after the start of the test. The likely explanation for this difference between the two methods is that urine flow increased initially after intravenous frusemide but was later impeded in some kidneys by an increasingly intense diuresis exerting an obstructive effect. During standard diuresis renography the early increase in urine flow was probably sufficient to cause elimination of tracer from these kidneys before the full obstructive effect of the diuretic had taken place. Although only one kidney in the study was totally obstructed when renography was performed 15 min after administering frusemide, another five kidneys showed very slow tracer elimination. Delayed elimination was also seen in another seven kidneys. Overall, 37% of the 35 kidneys were classified as obstructed on the basis of the results obtained with modified diuresis renography.

Although none of the standard diuretic renograms in this study clearly confirmed obstruction on direct inspection, a number of them showed equivocal responses. These equivocal curves arise because there is no clear demarcation between the "obstructive" and "non-obstructive" types of response pattern. In an attempt to overcome this difficulty, O'Reilly *et al.* (1978) introduced the DEI to quantify the change in the third phase of the renogram resulting from the effect of the diuretic and suggested a value of less than 30% as indicating obstruction, with higher values occurring in non-obstructive dilatation. These values, however, were calculated for non-background subtracted probe renography and cannot be applied to diuretic renograms derived from modern gamma camera/computer systems in which the background component is usually subtracted.

Gamma camera renography was employed in the present study using ^{123}I hippuran and it was felt on analysis of the renograms that a DEI greater than 45% clearly indicated a non-obstructive response pattern in all cases. Equivocal renograms had a lower DEI, the majority ranging from 35 to 45%. Based on this assessment, 3 of 22 kidneys non-obstructed on standard diuresis renography were obstructed on the modified test, including one kidney showing absent elimination of tracer during the latter test.

Ten of 13 kidneys with equivocal responses were also clearly obstructed during the modified test.

These results show that standard diuresis renography is a useful test for evaluating most cases of idiopathic hydronephrosis provided strict criteria are observed for determining when a response pattern is non-obstructive. Using ^{123}I hippuran with background subtracted renography, non-obstructed kidneys generally have a DEI greater than 45%. However, some kidneys with obstructive hydronephrosis also exhibit a DEI within this range but can be correctly assessed if the diuretic is given 15 min before the renogram. This modified approach to diuresis renography will also usually serve to clarify most cases in which an equivocal response pattern is seen on the standard test. It is for these reasons that we suggest that symptomatic patients should be reassessed by the modified test if obstruction is not confirmed by standard diuresis renography.

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Skeletal Anomalies Associated with Unilateral Renal Agenesis

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Summary—Unilateral renal agenesis is sometimes associated with skeletal anomalies The skeletal malformations are easily detectable and, if found, should suggest further urological investigations. The embryological aspect of the association is explored. Two cases are presented and the relevant literature is reviewed.

Aristotle was the first to describe congenital unilateral renal agenesis (URA). Collins (1932) reviewed 572 reported cases and found associated skeletal anomalies in 22 (3.8%). Jancu *et al.* (1976) reported two cases of URA associated with skeletal anomalies. In the past 6 years we have treated 45 patients with URA, two of whom had associated skeletal anomalies.

Patients and Methods

The first patient, a 32-year-old male, presented with pain in the right loin and hypertension of 3 years' duration. Neither X-ray nor intravenous urogram visualised the left kidney. Cystoscopy revealed hemitrigone with an absent left ureteric orifice and aortography confirmed the absence of the left kidney. The right renal artery and kidney were normal. Physical examination revealed a hypoplastic right thumb and funnelling of the lower chest below and medial to the nipples. X-rays showed a hypoplastic first right metacarpal with absent phalanges (Fig. 1) and deficient ends of the fifth, sixth and seventh ribs bilaterally. The patient has remained well on anti-hypertensive treatment.

The second patient, a 21-year-old male, presented with pain in the right loin. X-rays revealed non-obstructing right renal calculi with non-visualisation of the left kidney. Ultrasound did not show a left kidney. Cystoscopy revealed hemitrigone with an absent left ureteric orifice. Physical examination revealed facial asymmetry with a prominent left maxilla (Fig. 2), malformed ears, pes cavus and funnelling of the lower chest. X-ray revealed spina bifida S1. He underwent right pyelolithotomy and is asymptomatic.

Discussion

URA is found once in every 1500 intravenous urograms and once in every 1000 necropsies (Longo, 1952). It is known to be associated with congenital anomalies of other systems but rarely with skeletal anomalies (Thompson and Lynn, 1966).

Collins (1932) reviewed 572 cases of URA and found primary skeletal anomalies in 22 (3.8%). They included cleft palate, absent nose, absent patella, hydrocephalus, talipes equinovarus, *etc.* He did not say whether or not skeletal anomalies were the only associated malformation. Emmanuel *et al.* (1974) reviewed 74 patients with URA and found five with deformed spine and hemivertebrae. In three cases the URA was associated with hypoplastic thumb, anal atresia, vertebral anomalies, oesophageal atresia and T.O. fistula. In all cases the solitary kidney was discovered during investigation for some other condition and the skeletal anomalies were not identified as pointers to possible renal agenesis.

Jancu *et al.* (1976) reported two patients with

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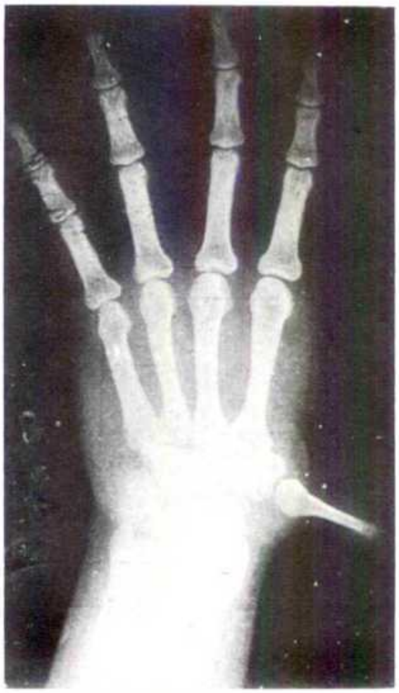

Fig. 1 Case 1. X-ray of hands shows right hypoplastic first metacarpal with absent phalanges.

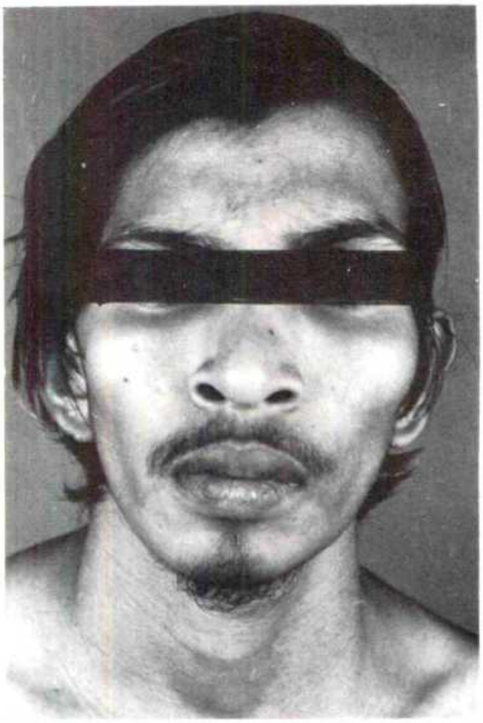

Fig. 2 Case 2. Note facial asymmetry with prominent left maxilla.

multiple anomalies, some of which were skeletal. One patient had rudimentary first ribs, hypoplasia of the radius, navicular and major and minor multiangular bones of the right arm, and aplasia of the thumb and first metacarpal bone. The other patient had duplication of proximal and distal phalanges of the right thumb with marked broadening and cutaneous syndactyly together with a hypoplastic first sacral vertebra.

In a review of 45 patients with URA seen during the last 6 years, we have found two (4.4%) with skeletal anomalies. They were unique in that they had URA which was associated with anomalies of the skeletal system only. Although the skeletal malformation might point to an associated renal anomaly, both patients presented with symptoms referable to the urinary system.

Visceral malformations associated with limb and vertebral anomalies have been observed among members of the luxoid group of mouse mutants such as dominant hemimelia (Dh) mutants (Say and Gerald, 1968).

Although it may be possible to relate malformations of the caudal end of the spine to imperforate anus and possibly to urogenital anomalies, the anomalies in both of our patients were not confined to the sacrum but involved ribs, thumb and facial bones. The explanation could be a mesodermal defect. Chromosomal studies could be done in the future on such patients to evaluate the possible role of genetic factors.

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Long-term Results of Conservative and Surgical Management of Blunt Renal Lacerations

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Summary—In the management of renal lacerations most attention has centred on surgical or non-surgical treatment and little attention has been given to the long-term results. We have evaluated the medical records and radiographs of 70 patients with blunt renal lacerations; 30 had initial non-surgical management and 40 had initial surgical management. Patients with initial non-surgical management were followed up for an average of 40.4 months. Normal blood pressure and/or radiological evaluation of the kidney were noted in 22% of those who had non-surgical management (hypertension in 55%) and in 75% of those who had delayed renal surgery (hypertension in 29%). Patients with immediate surgical management were followed up for an average of 49.6 months and normal blood pressure and/or radiological evaluation of the kidney were present in 83% (no hypertension). On long-term follow-up, patients with non-surgical management had a much higher rate of hypertension and/or abnormal radiological evaluation of the kidney than those with immediate surgical management.

There is general agreement on conservative management for renal contusion and on surgical management for renal rupture (shattered kidney) and for major renal pedicle injury, but the management of renal lacerations remains controversial. Some claim that renal lacerations almost characteristically restore themselves to normal while others feel that surgical management is needed. Little attention has been paid to the long-term results of these treatments and conflicting results have been found in the few published studies (Grant *et al.*, 1971; Slade, 1971; Pryor and Williams, 1975; Lipsky *et al.*, 1976). The medical records and radiographs of 70 patients admitted with blunt renal lacerations were evaluated to determine the long-term results of non-surgical and surgical management.

Patients and Methods

From 1959 to 1983 1522 patients were admitted with renal injury and 121 were diagnosed as having renal lacerations. Ten patients died on admission or on the operating table, having had no investigation or treatment of the renal laceration. Seventy of the remaining 111 patients had blunt renal lacerations and their medical records and radiographs were evaluated to assess their symptoms and signs, radiological evaluation, associated injuries, management and follow-up.

The indications for the initial infusion or large dose intravenous urography (IVU) were macroscopic or microscopic haematuria and/or pain, tenderness or mass in the side of abdomen or flank following trauma. A perirenal haematoma found during laparotomy for associated intra-abdominal injury was another indication for an IVU. Before 1970 the IVUs were performed after surgical treatment of associated injuries and the treatment of the renal lacerations was mainly conservative. After 1970 the IVU was performed while surgery for associated injuries was in progress by using a radiographic table top on an operating room table and treatment of the renal lacerations was mainly surgical (Cass *et al.*, 1971).

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Table 1 Sex and Age

		Immediate surgery No. (%)	*Conservative No. (%)*
Sex			
	Male	29 (72.5)	25 (83)
	Female	11 (27.5)	5 (17)
	Total	40	30
Age			
	0-19	14 (35)	10 (33)
	20-39	21 (52.5)	12 (40)
	40-59	4 (10)	6 (20)
	60 and over	1 (2.5)	2 (7)
	Total	40	30

Renal laceration was diagnosed on radiological evaluation by extravasation, a defect in the renal parenchyma and/or its vasculature or a split kidney with intrarenal and perirenal haematoma. A renal laceration was also diagnosed at renal exploration or at autopsy. Further investigations or procedures to diagnose renal laceration when the initial IVU showed indeterminate findings were repeat IVU, retrograde urography, renal arteriography, CT of the kidney, except during a laparotomy when renal exploration was performed for indeterminate IVU findings.

The follow-up status of the surgically and conservatively managed patients was determined by clinical status, blood pressure, IVU, isotope renography or CT of the kidney. Hypertension was defined as 160 mmHg or more systolic, 95 mmHg or more diastolic, or both.

Sex and age distribution were similar in both groups (Table 1).

Traffic accidents caused 27 lacerations (67.5%) treated by immediate surgical management and 18 (60%) treated conservatively. A fall, blow or crush caused 6 lacerations (15%) treated by immediate surgical management and 12 (30%) treated conservatively. Sporting accidents caused 7 lacerations (17.5%) treated by immediate surgical management.

Table 2 Degree of Haematuria

	Immediate surgery No. (%)	*Conservative No. (%)*
Not present	0	5 (17)
0-8 RBC/HPF	0	0
8-30	0	0
30-50	4 (10)	3 (10)
Packed/gross	24 (60)	9 (30)
Present-degree not known	12 (30)	13 (43)
Total	40	30

Table 3 Initial IVU Findings and Subsequent Investigations to Make Diagnosis

	Immediate surgery	*Conservative*
Normal	0	2^{A}
Non-function	10	1^{B}
Extravasation	14	10
Incomplete filling	12	12^{C}
Delayed visualisation	3	1^{D}
Not done	1	4^{E}
Total	40	30

A. Autopsy finding 2.
B. Delayed exploration 1.
C. Retrograde urogram 2; arteriogram 4; arteriogram + CT 1; arteriogram + delayed exploration 5.
D. Arteriogram 1.
E. Autopsy finding 4.

The degree of haematuria is shown in Table 2. No haematuria was present in 5 patients (17%) treated conservatively.

The initial IVU findings and subsequent investigations and procedures to diagnose the renal lacerations are shown in Table 3.

Results

Details of treatment are given in Table 4. With immediate surgical management the nephrectomy rate was 20% (8 of 40 patients). With initial non-

Table 4 Treatment

Treatment	*Immediate surgery*	*Conservative*
Non-surgical	—	22
Immediate nephrectomy	8^{A}	—
Immediate partial nephrectomy	13	—
Immediate suture	18	—
Immediate exploration/drainage	1	—
Delayed nephrectomy	—	2^{B}
Delayed partial nephrectomy	—	5
Delayed suture	—	1
Total	40	30

A. Pedicle injury + laceration 2; split kidney midpart 5; laceration hilum 1.
B. Underlying carcinoma kidney 1.

Table 5 Follow-up (FU) of Blunt Renal Lacerations

	Immediate surgery (40)				*Conservative (30)*			
Treatment	*No FU*	*FU (mths)*	*Blood pressure*	*Radiological evaluation*	*No FU*	*FU (mths)*	*Blood pressure*	*Radiological evaluation*
Non-surgical			—		14	49.8	Normal 5/11 >160/95 6/11‡	Normal 5/13 Polycystic kidney 1/13 Scarring/defect 4/13 Reduced function 3/13†
Immediate nephrectomy	5	43.1	Normal 5/5	Normal 3/3			—	
Immediate partial nephrectomy	13	88.0	Normal 10/10	Normal 11/13 Hydronephrosis 2/13			—	
Immediate suture	16	23.7	Normal 13/13	Normal 10/13 Small pole 1/13 No function 2/13				
Immediate exploration drainage	1	1.0	Normal 1/1	No function 1/1*				
Delayed nephrectomy			—		2	15.3	>160/95 2/2§	
Delayed partial nephrectomy			—		5	24.5	Normal 4/4	Normal 5/5
Delayed suture			—		1	40.0	Normal 1/1	Normal 1/1
Total	35 (plus 4 dead and 1 no FU)				22 (plus 7 dead and 1 no FU)			

* Renal arteriogram—renal artery occlusion
† One patient required partial nephrectomy at 5 months for severe hypertension
‡ BP 170/96—50 years old, 162/82 43 years old, 170/110 47 years old, 136/110 41 years old, 160/112 27 years old, degree not stated 17 years old
§ BP 140/100 46 years old; 160/102 67 years old.

surgical management six patients died within 4 days of injury (four on the first day after injury) and the renal laceration was found at autopsy. In the 24 surviving patients conservative management resulted in healing of the kidney in 16 (67%), while eight (33%) required delayed renal surgery, including two delayed nephrectomies (8%).

With immediate surgical management there were four deaths (two in hospital and two after discharge) and one patient had no follow-up (Table 5). The remaining 35 patients were followed up for an average of 49.6 months and 29 (83%) had normal blood pressure and/or radiological evaluation of the kidney (no hypertension). With conservative management there were seven deaths (six in hospital and one after discharge) and one patient had no follow-up.

The remaining 22 patients were followed up for an average of 40.4 months and normal blood pressure and/or radiological evaluation of the kidney were present in three of the 14 patients (22%) who had non-surgical management (hypertension in six of 11 patients (55%)) and in six of the eight patients (75%) who had delayed renal surgery (hypertension in two of seven patients (29%)).

Discussion

Although the early results of any treatment are important, the final test of its value is the long-term result. Normal blood pressure and/or radiological evaluation of the kidney were present in 83% of the patients followed up for an average of 49.6 months after immediate surgical management (no hypertension) compared with 22% of the patients followed up for an average of 49.8 months after non-surgical management (hypertension 55%). When delayed renal surgery was required following initial non-surgical management, normal blood pressure and/or radiological evaluation of the kidney were present in 75% of the patients followed up for an average of 24.1 months (hypertension 29%).

Grant *et al.* (1971) found that 13 of 33 patients developed hypertension, some after several years, when renal trauma was managed conservatively. The IVU was abnormal in 12 and the arteriogram abnormal in 11 of these 13 patients. Slade (1971) reported a 1 to 15-year follow-up on 32 patients with clinically severe renal injuries managed conservatively; 14 had abnormal IVUs but only one had hypertension. Pryor and Williams (1975) found that all 12 patients with severe renal injuries managed conservatively developed abnormal IVUs on follow-up and the five patients having arteriography showed severely damaged kidneys. Lipsky *et al.* (1976) reported a 1 to 17-year follow-up of eight patients with severe renal injuries managed conservatively and 13 managed with early surgery. Six of the eight patients managed conservatively had hypertension and radiological evaluation showed parenchymal shrinkage in six, pelviureteric junction stricture in one and calcification in the upper pole in one patient. Four of the 13 patients with early surgical management developed hypertension and two showed parenchymal shrinkage on IVU.

It is concluded from this study that patients with blunt renal lacerations who are treated conservatively have a higher rate of hypertension and/or abnormal radiological evaluation of the kidney than patients who receive immediate surgical treatment.

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An Ecological Study of Infected Urinary Stone Genesis in an Animal Model

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Summary—Direct molecular and morphological techniques of modern microbiology were used to monitor the sequential development of bacterial microcolonies and biofilms in a rat model of urinary infection and to demonstrate that the urease activity of the infecting organisms sets in course a series of reactions in which struvite and apatite crystals develop within the matrix of the enlarging bacterial aggregate. This forms multiple stone nidi on the uroepithelial surface upon which succeeding bacterial biofilms develop and with the incorporation of other urine components, such as urinary mucroproteins, establishes a matrix skeleton that becomes mineralised, thus allowing for the growth of the stone in concentric layers.

To arrive at this hypothesis, we studied infection stone genesis using a newly developed model for infection-induced bladder stone formation in the rat. We examined in detail the sequential events in the evolving microbial ecology of progressive struvite calculogenesis, using conventional microbiological techniques, direct ultrastructural observation, newly developed ultrastructural cytochemical localisation techniques and immunological procedures for stabilisation of the biofilm glycocalix and stone matrix in the rat model. It was concluded that the organic glycocalix material secreted by the associated bacteria comprises a substantial and aetiologically important part of the infection stone calculogenesis and matrix production.

P 35,551

Infection or struvite stones account for 15 to 20% of all urinary stones (Westbury, 1974; Griffith and Klein, 1983) and represent a significant health problem. Although bacterial association with struvite production has been recognised for decades (Hellstrom, 1938) and the stoichiometry of struvite crystallisation has been well defined (Griffith *et al.*, 1976a), the literature still reflects a paucity of knowledge in their aetiology, especially with regard to crystal aggregation, localisation and matrix production. With advanced techniques of scanning and transmission electron microscopy we have previously examined the ultrastructural microbiology of an infected calculus and demonstrated that the bacteria associated with this stone were present in a biofilm mode of growth adherent to the surface of the calculus (Nickel *et al.*, 1986). Using similar techniques, we studied the ultrastructural microbial ecology of a series of infected struvite calculi, surgically removed from patients, and implicated this bacterial biofilm mode of growth specifically with initial struvite crystallisation, matrix production and stone growth (Nickel *et al.*, 1985a).

As part of the continuing investigation we then examined the initial events in the *in vitro* production of infection stones (McLean *et al.*, 1985a). Based on these observations, we formulated the following hypothesis: invading ureolytic pathogens such as *Proteus mirabilis* colonise kidney epithelial cells and form glycocalix-enclosed microcolonies that eventually develop into continuous biofilms. The urease activity of the adherent bacteria creates an alkaline urine, causing precipitation of struvite and apatite crystals. The bacterial biofilm matrix or glycocalix

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serves to trap these crystals and other components present in the urine such as mucoproteins. Therefore, the growth of the stone depends to a certain extent on the glycocalix material secreted by the surface biofilm of bacteria, with subsequent trapping of the struvite crystals induced by the localised urease activity resulting in concentric laminar growth.

Our hypothesis that the glycocalix material secreted by the associated bacteria may comprise a substantial and aetiologically important part of the infection stone calculogenesis and matrix production was still conjectural at the beginning of the present study. To test this hypothesis we studied infection stone genesis using a modification of a newly developed model for infection-induced bladder stone formation in the rat (Satoh *et al.*, 1984).

This report examines in detail the sequential events in the evolving microbial ecology of progressive struvite calculogenesis, employing conventional microbiological techniques, direct ultrastructural observation, newly developed ultrastructural cytochemical localisation techniques and immunological procedures for the stabilisation of the biofilm glycocalix and stone matrix in the rat model.

Materials and Methods

Animal model

Adult male Sprague-Dawley rats (weight 250–300 g) were obtained from an outbred colony of CRL: CD(SD) BR rats maintained at the University of Calgary. The rats were kept in polycarbonate box cages using corn cob bedding and were housed in quarters maintained at 20 ± 2°C, 30 ± 10% relative humidity and 12 h of daily illumination. They were provided with standard rat chow and tap water *ad libitum*.

Proteus mirabilis was obtained from a previously studied patient with struvite stones (Nickel *et al.*, 1985a). This *Proteus mirabilis* was also used for *in vitro* studies of struvite stone genesis (McLean *et al.*, 1985a). The bacteria were grown on TSB and then stored on nutrient agar. A 1% inoculum grown overnight in tryptic soy broth was prepared. Bacteria were washed twice with phosphate buffered saline, PBS (pH 7.2) and resuspended in tryptic soy broth. The inoculum concentrates were adjusted to 1×10^8 colony-forming units (CFU)/ml.

A modification of a previously reported procedure (Satoh *et al.*, 1984) was used in this experiment. Rats were anaesthetised and maintained under 4% halothane. The abdominal wall was thoroughly swabbed with 70% isopropyl alcohol and the bladder exposed through a small suprapubic incision. Two sterile zinc discs (0.36 ± 0.05 cm) were inserted into the bladder through a small vesical incision and the incision closed with running 4/0 chromic catgut. The peritoneal incision was closed with 4/0 sutures and the skin closed with autoclips. Post-operative antibiotics were not employed and no infections or mortality were observed following surgery. Seven days after surgery the rats were again anaesthetised with 4% halothane, the penile area was treated with 70% alcohol and the rats were catheterised with a lubricated sterile polyethylene tube and 0.2 ml of bacterial suspension containing 1×10^8 CFU/ml were injected into the bladder. Rats recovered in 1 to 2 min and were returned to their cages with food and water *ad libitum*.

A control group of animals, consisting of rats with surgically implanted zinc discs but uninfected with *Proteus*, was also used.

Experimental design

Rats were sacrificed daily by CO_2 intoxication, at days 0 to 8 as well as days 15 and 30 after inoculation. Urine, zinc discs (with adherent calculi), as well as sections of the bladder and kidney were obtained for CFU counts, pH measurement, quantitative urease activity, histological examination, scanning electron microscopy, transmission electron microscopy, ultrastructural urease localisation and antibody stabilisation studies. The dry weight of any calculus encrustation was also determined.

Urine was obtained from the intact bladder at the time of sacrifice by aspiration with a syringe and needle. The samples were then serially diluted and plated on 4% MacConkey agar. A representative number of discs and adherent crystals from each group were rinsed with PBS, placed in 1 ml sterile PBS and sonicated for 1 h. Aliquots were plated as above. The pH of the urine was determined with a standardised pH meter. Urease activity of the urine and disc was measured by suspending the disc or 0.2 ml urine into a buffered urea solution at 30°C. Following a 15-min incubation, the ammonia produced was determined colorometrically using the Weatherburn (1967) modification of the indophenol blue procedure. By subtracting the background ammonia present in a substrate (urea) minus a control, urease activity in a known volume was determined.

The disc and its associated stones were removed from the bladder at autopsy and dried in a dessicator for 24 h The weight of the stones was estimated by subtracting the initial weight of the disc from that of the disc and the stones together. The dried calculus material was then chemically analysed.

The bladder and kidney specimens prepared for histological studies were fixed in 10% formalin solution. After fixation the samples were sectioned and then stained with standard hematoxylin and eosin.

Disc surfaces were processed for scanning electron microscopy (SEM) using the procedures employed successfully by us to examine bacterial biofilm on struvite stones removed from infected patients (Nickel *et al.*, 1985a, 1986). Because processing for SEM presented a problem in that most of the struvite crystals tended to dissolve at neutral or acidic pH, we adopted measures for processing some of the specimens that reduced crystal loss. These specimens were dipped in 0.1 M TRIS buffer (pH 9.0) and allowed to air dry without fixation. SEM specimens were mounted on aluminium stubs, sputter-coated with a palladium-gold mixture, and examined as described previously. Confirmatory analysis of individual crystals observed in the ultrastructural study was performed with electron-probe X-ray microanalysis, EDAX (Hall and Gupta, 1983), using a Microspec model 711 apparatus.

For transmission electron microscopy (TEM) processing the encrusted discs were fixed overnight at 4°C in 5% glutaraldehyde buffered in 0.1 M cacodylate buffer (pH 7.2). All buffers used in TEM processing contained 0.15% (wt/vol) ruthenium red. Scrapings taken from these surfaces were enrobed in 4% agar (Difco) and processed as previously described (Nickel *et al.*, 1985a, 1986). Several specimens were subjected to ultrastructural examination for urease activity using a newly developed cytochemical urease localisation procedure (McLean *et al.*, 1985b). This technique involves precipitation of the urease end product (ammonia) with sodium tetraphenylboron. Subsequent replacement of the ammonia in the ammonium tetraphenylboron precipitate by silver allows electron-dense silver tetraphenylboron to serve as a marker for urease activity in transmission electron microscopy. This procedure allows localisation of urease activity within the bacterial biofilm.

Morphological stabilisation of the biofilm glycocalix and stone matrix with specific antibody was performed on a number of specimens. This technique has been previously described (Costerton, 1979; Mackie *et al.*, 1979). It involves exposing the washed encrusted disc surface to undiluted antisera for 1 h. The antisera were developed by serial injection of washed formalin-treated cultures of *Proteus mirabilis* into New England white rabbits. The immune response of the rabbits was monitored with a modification of the precipitin test (Rantz and Randall, 1955) and serum specificity for exopolysaccharide was monitored by counter immunoelectrophoresis (Costerton, 1979). The phosphate-buffered saline-washed surfaces were fixed in 5% glutaraldehyde in cacodylate buffer (0.1 M, pH 7.2) with 0.15% ruthenium red and processed for transmission electron microscopy as described previously (Nickel *et al.*, 1985a, 1986). Controls involved the same treatment except that pre-immune serum (drawn from rabbits before initiating the immunisation schedule) was used. Glycocalix-specific antibodies prevent the collapse of the highly hydrated glycocalix during dehydration for electron microscopy and this morphological recognisable "stabilisation" serves both to show the actual dimensions of this matrix and to identify it as being of bacterial origin.

Results

The uninfected control group of 20 rats showed no significant calculus formation on the implanted zinc discs. The dried weight of the material adherent to the control discs after 7 days was 0.005 g. The urine remained sterile, pH averaged 6.6 and urease activity was stable at approximately 2 µg N/ml/15 min of reaction time during the entire study period. No histological changes were noted in the bladder or kidneys of these animals.

The experimental group of 110 rats was studied sequentially with approximately 10 rats sacrificed per day for the first 8 days following bacterial inoculation. Two further groups of 10 rats each were sacrificed at 15 and 30 days respectively.

The experimental group demonstrated progressive calculus formation on the zinc disc (Fig. 1). The dry weight of the crystallisation material adherent to the discs slowly accumulated from 0.019 g/disc at 24 h after inoculation (Day 1) to

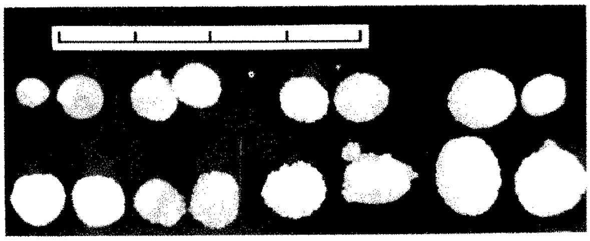

Fig. 1 The two zinc discs removed daily, demonstrating progressive calculus formation on the inert surfaces during the first 8 days after bacterial inoculation (Scale is in cm).

0.064 g/disc in 8 days and finally 0.13 g/disc in 30 days. The bacterial counts in the urine increased rapidly and remained at about 1×10^8 CFU/ml. There was some decline approximately 6 days into the experiment, possibly due to growth inhibition by the elevated pH or formation of microcolonies or aggregates within the urine. The disc itself became colonised by about 1×10^6 bacteria/cm^2 in 1 day and then declined somewhat, probably as a result of the formation of microcolonies (seen only as a single CFU per microcolony) within the developing stone. The pH also increased rapidly and stabilised between 7.01 and 7.07 for the duration of the experiment. Urease activity in the urine increased rapidly from control values and although the activities ranged from 8 to 28 μg N/ml/15 min reaction time, the values remained elevated for the duration of the experiment. The urease activity on the zinc disc also increased and again there was considerable variability between different rats within the same group as well as between rats sacrificed on succeeding days. The values ranged from 12 to 20 μg N/discs/15 min reaction time.

At 24 h refractile crystals were observed on the zinc discs. Grossly, the bladders and kidneys were normal; histologically, only the bladder demonstrated some acute inflammation. By 48 h the crystals were confluent on the disc surface and appeared to be embedded in a slime layer covering the foreign body. Examination at 72 h demonstrated definite calculus formation. Bladder wall thickening was observed and histologically the bladder demonstrated both acute and chronic inflammation. Five days after inoculation, growth of the calculi was observed. About 50% of the kidneys demonstrated acute pyelonephritis. By 15 days the stone had continued to enlarge, the bladder showed evidence of chronic inflammation, bilateral hydronephrosis was evident in 60% of the rats, and most had histological evidence of acute and chronic renal infection. When sacrificed at 30 days, all rats had developed large bladder calculi completely occluding the zinc disc (Fig. 1) and a few developed smaller "satellite" stones within the bladder that were not associated with the zinc disc. While all rats had bilateral hydronephrosis and pyelonephritis, a few (4 of 10) had developed large staghorn calculi within the renal pelvis (Fig. 2).

Chemical analysis of a stone from each series revealed that all calculi formed in this experiment were composed predominantly of struvite (magnesium ammonium phosphate) with about 5% of the stone weight being calcium (probably apatite).

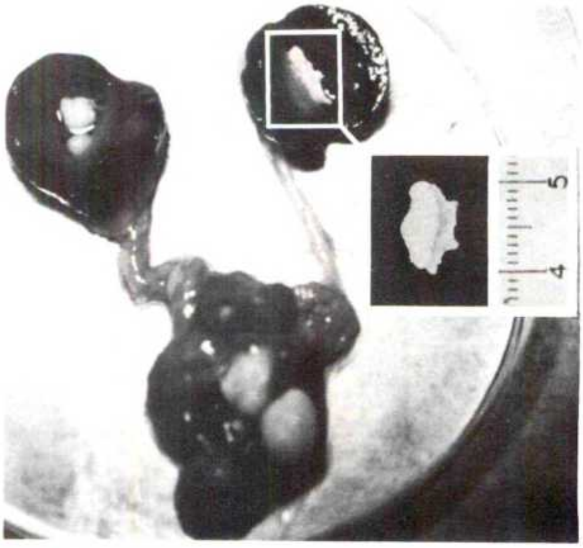

Fig. 2 A number of rats studied at 30 days had developed staghorn renal calculi as well as the typical bladder stones. Note that the renal calculus (inset) had formed a cast of the renal pelvis.

Detailed scanning electron microscopic examination of the disc removed 24 h after bacterial inoculation showed an extensive bacterial biofilm colonising the surface, within which rod-shaped bacterial cells were embedded in the dehydration-condensed remnants of their glycocalix matrices (Fig. 3). Forty-eight hours after bacterial inoculation, crystals morphologically typical of struvite and apatite were seen in association with these bacteria. The crystals from the infected series of animals were covered by an amorphous substance within which rod-shaped bacteria were present (Fig. 4) and energy-dispersive X-ray analysis of these biofilm-covered crystals (Fig. 5) revealed the presence of magnesium, calcium and phosphate, which would suggest the presence of struvite and apatite. Sequential scanning ultrastructural studies of the disc surface showed consolidation of the individual crystals into a macroscopic stone, entrapping bacterial microcolonies within it as it grew. The developing stone surface remained covered by a thick bacterial biofilm in which bacteria were enmeshed within a dehydrated fibrous organic matrix that appeared to permeate the crystalline aggregate (Fig. 6).

Transmission electronic microscopy of material obtained from the stones by vigorous scraping showed gram-negative bacterial cells within an anionic fibrous matrix (Fig. 7) composed of the dehydration-condensed residues of their exopolysaccharide glycocalices. Exposure of encrusted

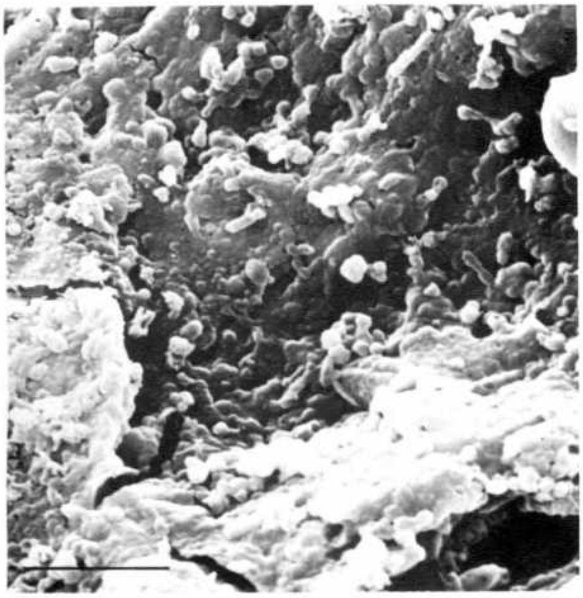

Fig. 3 SEM of the surface of a zinc disc 24 h after bacterial inoculation, showing adherent bacterial cells surrounded by the dehydration-condensed remnants of their fibrous glycocalices. These adherent organisms constitute a developing bacterial biofilm. Bar = 5 μm.

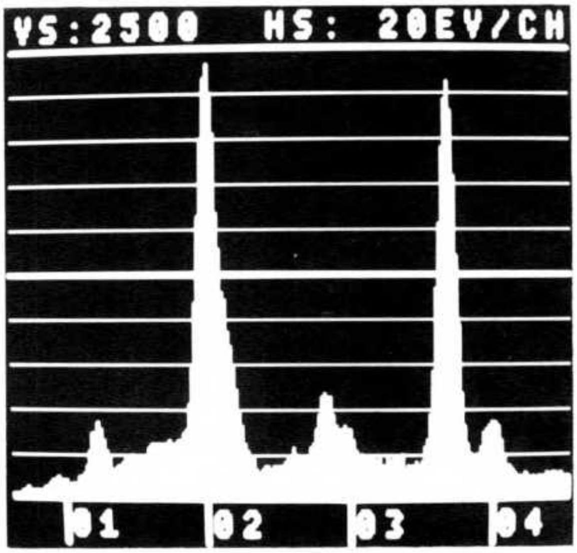

Fig. 5 EDAX profile of the crystals underlying the biofilm seen in Figure 6, showing the composition (Mg, P, Ca) of these crystals which is consistent with their identity as struvite ($MgNH_4PO_4 . 6H_2O$) and carbonate-apatite ($Ca_{10}(PO_4)_6 . CO_3$).

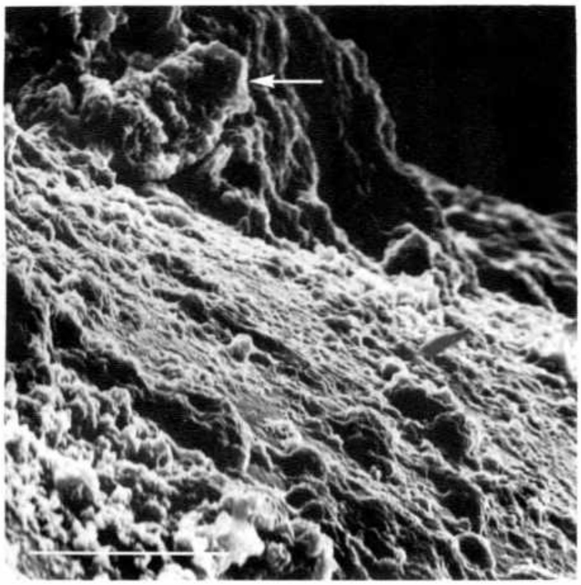

Fig. 4 SEM of the surface of a zinc disc 96 h after bacterial inoculation, showing the presence of a coherent bacterial biofilm, within which rod-shaped bacterial cells can be seen (arrows) covering the developing crystals in this complex accretion. Most of the bacteria in this mature biofilm are "buried" in the dehydration-condensed remnant of their glycocalices. Bar = 5 μm.

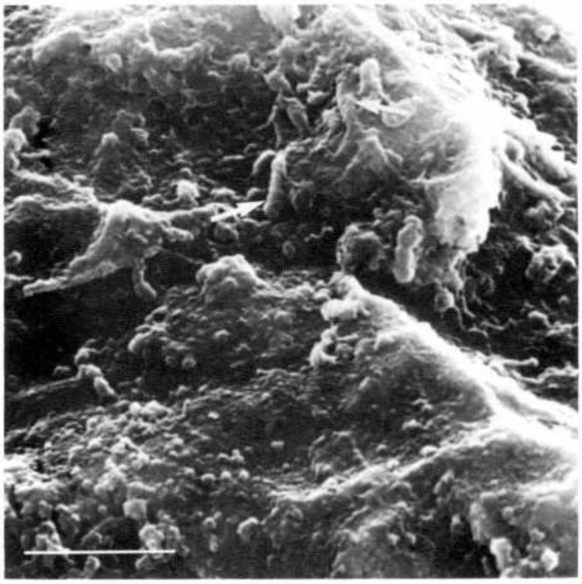

Fig. 6 SEM of the surface of a zinc disc 168 h after bacterial inoculation, showing areas where crystals predominate (white arrow) and areas covered with a very thick amorphous biofilm within which some bacterial profiles can be resolved at higher magnification. Bar = 40 μm.

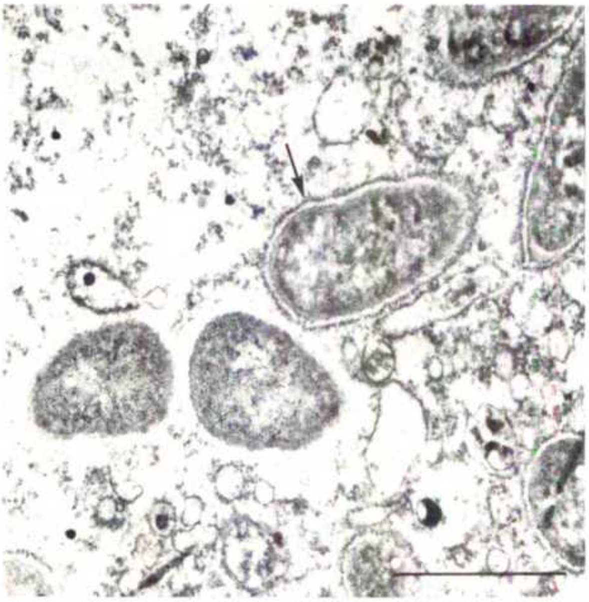

Fig. 7 TEM of a ruthenium red stained preparation of material scraped from the surface of developing struvite crystals on a zinc disc 72 h after bacterial inoculation. Gram-negative bacterial cells are seen to be surrounded by the fibrous dehydration-condensed remnants of their glycocalices, which show a concentric dense structure (arrow) immediately outside the triplicate outer membranes of the cell walls of some cells. Bar = 1 µm.

surfaces to solutions of acidic pH used in transmission electron microscopy specimen preparation caused the attached crystals to loosen and eventually dissolve, leaving gaps within the stone matrix (Fig. 8). The stratification effect of succeeding layers of bacterial biofilms sandwiched between the crystallised zones can be clearly seen in demineralised TEM preparations (Fig. 9). When the biofilm and matrix material was scraped from the disc surface and stained with ruthenium red after stabilisation with specific antibody, it was evident that the cells of *Proteus mirabilis* and the struvite crystals within the biofilm were embedded in an extensive fibrillar matrix of bacterial origin (Fig. 10).

Ultrastructural urease localisation (Fig. 11) demonstrated a great deal of urease activity which was clearly associated with the neighbouring bacterial microcolonies, resulting in local deposition of product (ammonia) within the fibrillar matrix of the bacterial biofilm and consequently within the stone matrix.

Discussion

Modern crystallographic analysis (Griffith, 1978) has shown that human "infection" stones are a mixture of struvite, a crystalline substance com-

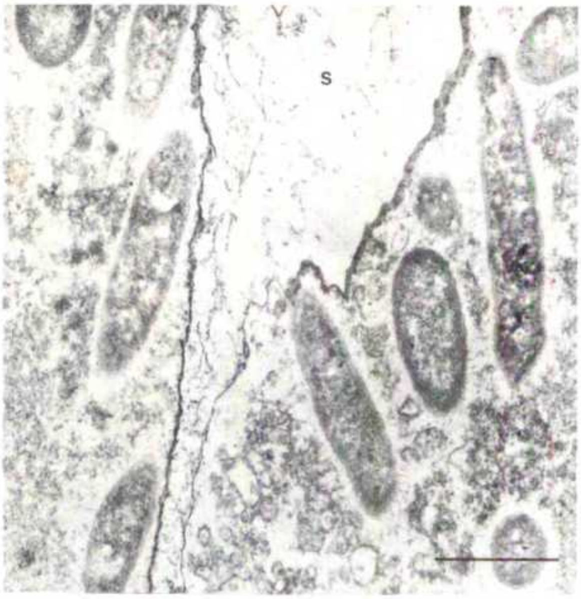

Fig. 8 TEM of a ruthenium red stained preparation of material scraped from the surface of a zinc disc 48 h after bacterial inoculation. Gram-negative bacteria are clearly seen within the fibrous dehydration condensed matrix of the biofilm but the struvite crystals, seen here as an angular empty space (s), have been dissolved by the acidic solutions used in preparing samples for TEM. Bar = 1 µm.

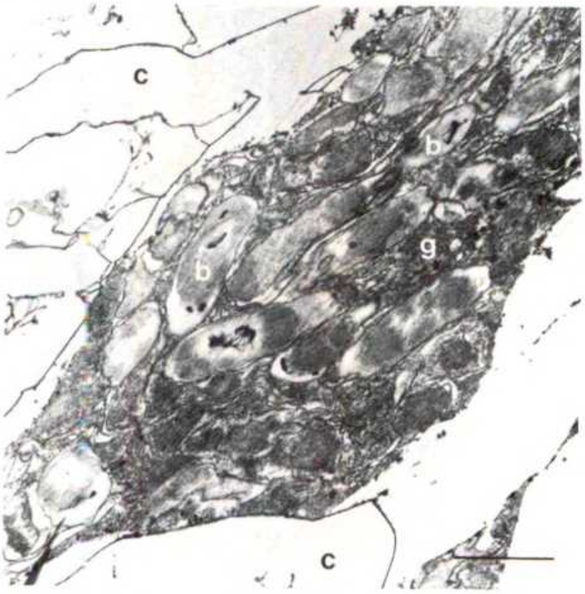

Fig. 9 TEM of material scraped from the surface of a zinc disc 168 h after bacterial inoculation. Gram-negative bacteria (b) within their glycocalix (g) enclosed biofilms are seen to be sandwiched between crystalline areas (c) seen here as demineralised spaces. This preparation clearly shows the stratification effect of the successive surface biofilms and their association with subsequent crystallisation.

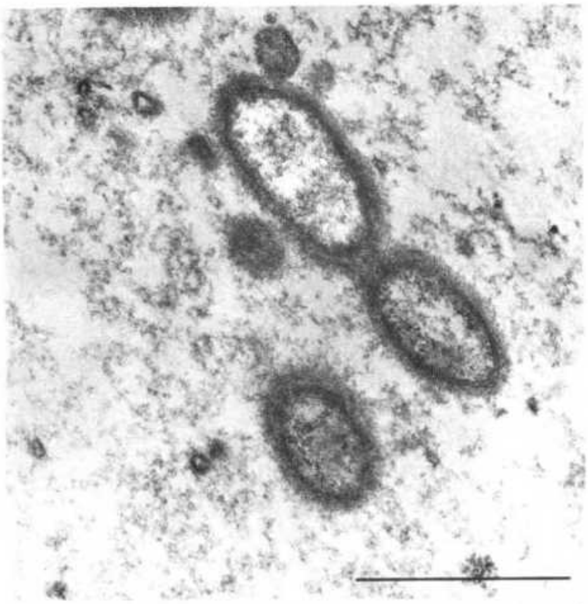

Fig. 10 TEM of a ruthenium red stained preparation of antibody-stabilised biofilm scraped from the surface of a zinc disc 48 h after bacterial inoculation. The stabilisation of the fine fibrillar glycocalix material surrounding the Gram-negative bacteria, and partially filling the intercellular spaces of the biofilm, shows that these cells are immunologically identical to the *Proteus mirabilis* strain used to raise the stabilising antibodies and that the biofilm matrix is composed of these finely fibrillar bacterial exopolysaccharides. Bar = 1 μm.

posed of magnesium ammonium phosphate ($MgNH_4PO_4 \cdot 6H_2O$) and carbonate-apatite ($Ca_{10}(PO_4)_6 \cdot CO_3$). Although the cause and effect relationship between urinary infections and stones has been established since the turn of the century (Horton-Smith, 1897; Brown, 1901) and although urease activity was suggested as the aetiological basis of infection stones over 50 years ago (Hagar and Magrath, 1925; Sumner, 1926), our knowledge of infection stones has advanced little since Hellstrom (1938) confirmed this generally recognised distinction between "aseptic stones" and "infection stones" by demonstrating bacteria within the interstices of infection calculi by light microscopy. The stoichiometry of the actual crystallisation process, however, has been well worked out.

In a series of *in vitro* experiments, Griffith *et al.* (1976a) demonstrated that infection-induced ureolysis increases urinary levels of ammonia, bicarbonate and carbonate, as well as urinary pH which brings about urinary supersaturation with respect to struvite and carbonate-apatite, resulting in crystal formation. The production of alkaline urine is, however, insufficient to cause a rate of crystal aggregation that would account for mature stone formation (Rose, 1982; Griffith and Klein, 1983). In order to form a macroscopic and therefore clinically significant stone, a second factor or "matrix" is required which will cause the particulate matter to bind together. In fact there is a poorly

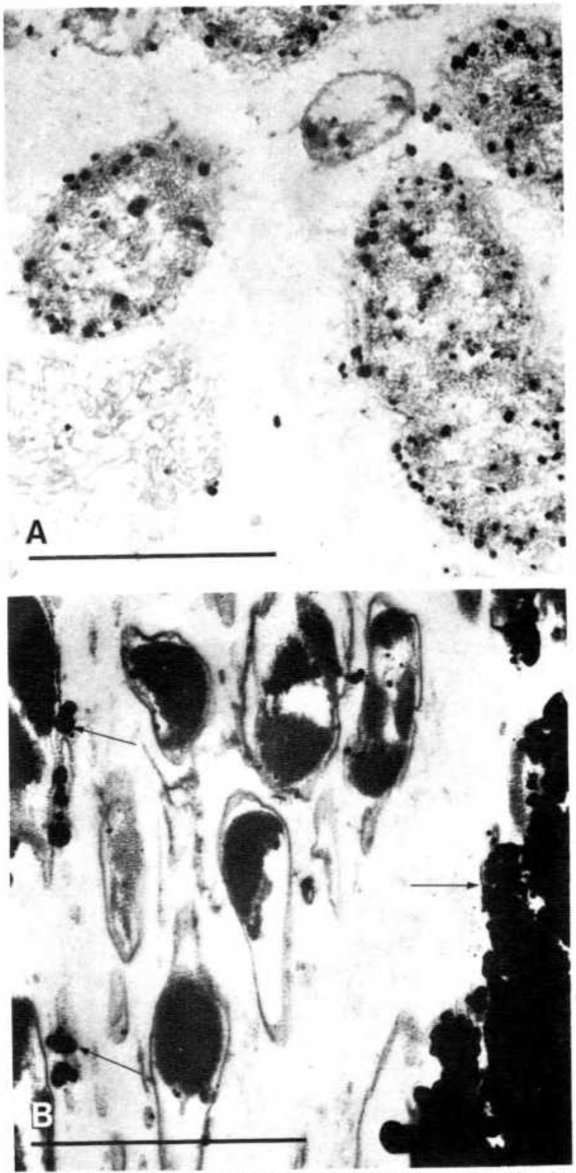

Fig. 11 (A) TEM of material scraped from the surface of a zinc disc 48 h after bacterial inoculation. This bacterial biofilm served as a control preparation for urease localisation, in that no substrate (urea) was supplied, but residual urea and background ammonia levels produced some electron-dense, cell-associated silver tetraphenylboron crystals. (B) TEM of material scraped from the same zinc disc seen in Fig. 11 (A) and incubated with substrate (urea) to localise urease activity. Very extensive deposits (arrows) of electron-dense silver tetraphenylboron crystals attest to the vigorous urease activity of bacterial cells within this biofilm.

understood organic matrix that commonly occurs in association with these stones (Wickham, 1976, 1982; Griffith and Klein, 1983) and the amount of organic material present in infection stones is larger than that in metabolic stones (Williams, 1979). Several investigators (Finlayson *et al.*, 1961; Griffith *et al.*, 1976b; Griffith, 1978) have discovered an increase in urinary mucopolysaccharides and mucoproteins in urinary infections with urease positive bacteria. These substances sometimes coalesce to form matrix concretions or matrix stones (Allen and Spence, 1966) composed of mucoproteins, carbohydrates, cellular debris and crystals of struvite and apatite (Boyce and Garvey, 1956). It is generally felt that these matrix concretions contribute to calculogenesis in an incompletely defined manner, probably forming the matrix backbone of the "mature" infected stone (Allen and Spence, 1966; Wickham, 1976). The origin of this organic matrix material is unknown (Wickham, 1976; Rose, 1982; Griffith and Klein, 1983) and while it has been suggested that it results from mucosal or renal irritation by the infecting organism (Griffith, 1978; Griffith and Klein, 1983), there is no evidence that the organic matrix is primarily derived from the transitional epithelium or from serum mucoproteins (Wickham, 1982).

Wickham (1976) also observed that in the infection-induced system of calculogenesis, there is no evidence of disturbed renal metabolism, no intracellular matrix precursor and no intratubular matrix precursors. Stanton-King and Boyce (1963) demonstrated that marked crystalline accretion could be produced in an experimental system deliberately infected with urea-splitting organisms even when the stone fragment was totally isolated from the urine in a sealed dialysis sac. In this experiment both mineral and matrix deposition appeared biochemically and microscopically indistinguishable from that found in the naturally occurring *in vivo* calculi, thus demonstrating that a supply of urinary macromolecules is not essential for calculus development. This implicates the bacteria themselves in the deposition of matrix material and others (Wickham, 1976; Rose, 1982) have since proposed that the infecting bacteria either cause increased uromucoid in the urine, or aggregation, or both, but until recently there was no practical evidence to substantiate this.

In two previous studies (Nickel *et al.*, 1985a, 1986) we employed direct morphological examination of surgically removed struvite stones with scanning and transmission electron microscopy, and demonstrated that the struvite calculi contained large numbers of bacterial cells that grew within extensive fibrous anionic matrices produced by the bacteria themselves. In these studies the bacterial cells and their products were implicated in calculogenesis by appearing to provide at least a part of the matrix and a means of aggregation of magnesium ammonium phosphate crystals to form macroscopic struvite stones. When we examined the initial events in struvite stone production, using an *in vitro* technique (McLean *et al.*, 1985a), it appeared that the early glycocalix-enclosed bacterial biofilm provided an initial focus for crystal development and stimulated further growth into a macroscopic calculus.

In this present *in vivo* animal model study it was noted that a bacterial biofilm consisting of the bacteria and their associated glycocalix material developed on the zinc disc. Ultrastructural localisation of urease activity demonstrated local deposition of ammonia from the ureolysis of urea within the biofilm matrix. The local area within the biofilm matrix would become alkaline, eventually followed by the urine itself. This local alkaline environment with high ammonia concentration would result in a precipitation of struvite and apatite crystals which would become entrapped in the bacterial biofilm matrix. Stabilisation by specific antibodies has shown that the fibrous matrix seen during early crystallisation and nidus formation is indeed of bacterial origin. The highly hydrated bacterial glycocalix (99% water) which forms the initial stone matrix is often underestimated because it condenses radically during dehydration for electron microscopy (Sutherland, 1977) unless stabilised by specific antibody (Costerton, 1979; Mackie *et al.*, 1979). Continued ultrastructural examination of the growing stones in the rat model indicates that the nidus formed from the original crystal aggregation grows as succeeding surface biofilms of bacteria secrete their glycocalices, with subsequent further entrapment of struvite crystals resulting from the localised urease activity. In fact, crystal-free regions or "matrix" areas are often found in the periphery of struvite stones (Wickham, 1982) and it is likely that matrix formation precedes mineralisation. Also, the matrix of infected stones tends to be arranged in concentric laminations around a central core with subsequent deposition of magnesium ammonium phosphate which creates the effect of tree-like growth rings (Wickham, 1982).

Clinically, the bacteria associated with struvite stones are notoriously resistant to eradication (Rocha and Santos, 1969; Nemoy and Stamey, 1971; Griffith, 1978; Rose, 1982; Griffith and

Klein, 1983; Fowler, 1984) and the infection is seldom controlled until the stone is removed. Long-term antibiotic therapy can be effective in controlling the incidence of urinary infection (Chinn *et al.*, 1976; Feit and Fair, 1979) but investigators have confirmed that bacteria remained viable in large numbers in the core of stones following antibiotic treatment (Rocha and Santos, 1969; Nemoy and Stamey, 1971, 1976) and, in fact, once antimicrobials are terminated, bacteriuria usually recurs. Using *in vitro* techniques we have previously demonstrated (Nickel *et al.*, 1985b) that bacteria growing in adherent biofilms in a urine milieu have a relative antibiotic resistance, despite favourable *in vitro* minimal inhibitory data, that appears to be related to the extensive glycocalix production by adherent microcolonies of bacteria.

Based on the observations in this study and on our previous clinical (Nickel *et al.*, 1985a, 1986) and *in vitro* (McLean *et al.*, 1985a; Nickel *et al.*, 1985b) investigations, we feel that the following hypothesis has some validity. The renal urine becomes infected with urea-splitting bacteria whose pili and glycocalices mediate their adhesion to the urothelium. There bacteria form adherent microcolonies that secrete an enveloping glycocalix that results in the development of a coherent bacterial biofilm on the uroepithelial surface. Crystallisation of struvite and apatite occur as a result of the enzymatic action of bacterial urease, with subsequent elevation of pH and deposition of ammonia within the organic matrix, forming multiple stone nidi. Succeeding bacterial biofilms develop on the surface of the developing stone and the incorporation of other urine components such as urinary mucoproteins establishes a matrix skeleton that becomes mineralised, thus allowing for the growth of the stone in concentric layers. The bacteria on and within the stone are protected from host defences and antibiotic therapy because of their glycocalix-enclosed microcolonial biofilm mode of growth. This hypothesis may help to explain the intimate involvement of ureolytic bacteria in matrix production, biofilm formation, antibiotic resistance, crystal nidus formation, localisation of the stone growth in the renal pelvis and in the subsequent growth of the calculi into mature staghorn configurations.

Acknowledgement

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Enkephalin Inhibits Presynaptically the Contractility of Urinary Tract Smooth Muscle

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Summary—The influence of methionine-enkephalin and leucine-enkephalin on human detrusor and on pig detrusor, trigone, bladder neck and urethral smooth muscle was investigated *in vitro*. The enkephalins inhibited the smooth muscle contractility presynaptically. Methionine-enkephalin was about 40% more potent than leucine-enkephalin.

Phentolamine-resistant contractions were less inhibited by the enkephalins than atropine-resistant contractions and contractions that were not blocked. The inhibitory nerve responses of the trigone, bladder neck and urethra were unaffected.

Methionine-enkephalin (M-enk) and leucine-enkephalin (L-enk) are closely related pentapeptides (Beaumont, 1983). The two peptides are localised to synaptic vesicles in nerve terminals in the central nervous system and in peripheral autonomic nerves (LaMotte and de Lanerolle, 1981; Miller, 1981). M-enk and L-enk appear in different nerve populations (Larsson *et al.*, 1979). Enkephalin nerves have also been demonstrated in lower urinary tract smooth muscle and in ganglia of the urinary bladder (Alm *et al.*, 1981; Booth *et al.*, 1981; Kawatani *et al.*, 1983).

The enkephalins are endogenous ligands for opiate receptors (Miller, 1981; Beaumont, 1983) and transmit almost exclusively inhibitory nerve responses (Iversen *et al.*, 1978; Konishi *et al.*, 1979; North *et al.*, 1979; Williams and North, 1979; Booth *et al.*, 1981). The function of various smooth muscles is modulated by enkephalins (Waterfield *et al.*, 1977; Uddman *et al.*, 1980; Aleixandre *et al.*, 1981; Hellström and Rosell, 1981; Petkov and Radomirov, 1982; von Wienbeck and Dünzen, 1982). Urinary bladder motility is depressed by enkephalin via activity on vesical ganglia (Booth *et al.*, 1981; Simonds *et al.*, 1983) and by intrathecal administration (Hisamitsu *et al.*, 1982). The same is found with intracerebrovascular microinjections of β-endomorphin (Dray *et al.*, 1984). Also, morphine depresses the detrusor and enhances the risk of urinary retention, especially if given intraspinally. Opiate antagonism with naloxone enhances detrusor activity in cats (Roppolo *et al.*, 1983), rats (Dray *et al.*, 1984) and humans (Murray and Feneley, 1982; Murray, 1983), suggesting enkephalinergic inhibitory control.

The aim of the present study was to explore the influence of enkephalin on lower urinary tract smooth muscle in a series of *in vitro* experiments.

Material and Methods

The bladder and urethra from 18 female Danish landrace pigs were removed in a slaughterhouse shortly after the animals had been killed by a blow to the neck and exsanguinated. Human detrusor muscle was obtained from 19 cystotomy cases. The specimens were dissected into strips of approximately 1 cm in length and 1 mm in diameter. The detrusor strips (46 from 19 humans and 20 from 10 pigs) were taken from the anterior part of the dome and the trigone strips (12 from six pigs) were taken in an oblique direction from the internal urethral orifice and medially to one of the ureteric orifices. The bladder neck strips (10 from five pigs) were transversal from the posterior half of the border-

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line between the bladder and the urethra. The urethral strips (six strips from three pigs) were longitudinal from the proximal posterior part.

The experiments were performed in Krebs solution bubbled with carbogen (95% O_2 and 5% CO_2) in a 3 ml chamber organ bath at 37°C. The tension was measured with Grass force-displacement transducers (model FTO3). The signals were amplified by a strain gauge transducer amplifier (frequency response 0-20 Hz, Herlev Medico-technical Laboratory) and recorded on a Watanabe SR-6312 servocorder.

A Dantec dual CC stimulator 14 E 10/11 was used for the electrical stimulations. Square wave pulses of 1 ms duration and in 5 s trains were delivered with an electric field strength of 0.15 kV/m.

Drugs were freshly prepared daily and added in volumes of 0.05 ml. The enkephalins and substance P (Peninsula Laboratory), prostaglandin $F_{2\alpha}$ (May and Baker) and tetrodotoxin (Sigma) were prepared from stock solutions stored at −22°C. Atropine sulphate (DAK), noradrenaline (DAK), phentolamine mesylate (CIBA), propanolol chloride (ICI) and sodium ketoprofen (Rhone-Poulenc) were prepared from vials. The Krebs solution was in mmol/l: Na^+ 143.4; K^+ 5.8; Mg^{++} 1.2; Ca^{++} 2.0; Cl^- 127.0; SO_4^{--} 1.2; HPO_3^- 25.0; HPO_4^- 1.2; glucose 10.1, pH 7.4.

The experiments were started after a baseline stabilisation period of at least 1 h. The baseline was adjusted to approximately 1 g. In experiments with electrical stimulation, enkephalin was added when the response was stable. In experiments with pharmacological stimulation, enkephalin was placed between two control stimulations in half of the experiments and with the control stimulation between two enkephalin-blocked stimulations in the other half.

Forty-six of the 94 strips were stored at 4°C for 24 h before investigation.

The Wilcoxon test for pair differences was used for the statistical calculations.

Results

Both M-enk and L-enk significantly inhibited electrically evoked contractions. Fig. 1 shows a human detrusor strip blocked with atropine and Fig. 2 shows a pig bladder neck strip. The median inhibition of the amplitude in percentage of the control contractions is given in the Table. M-enk was 1.4 times more potent than L-enk ($P<0.05$) and contractions evoked by 5 to 10 Hz stimulation were inhibited 1.5 times more than contractions evoked by 30 Hz stimulation ($P<0.01$). Contractions resistant to atropine were reduced 2.6 times more than contractions resistant to phentolamine ($P<0.01$) and contractions that were not blocked were reduced 2.5 times more than phentolamine-influenced contractions ($P<0.01$).

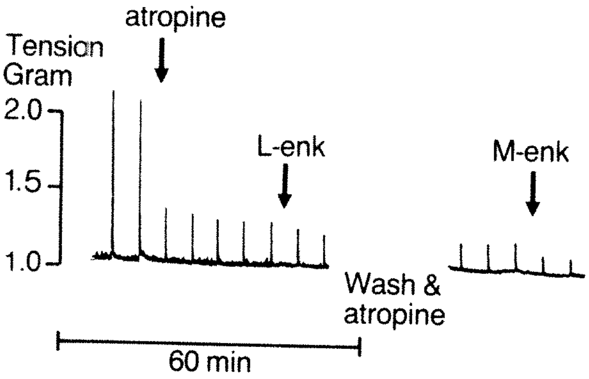

Fig. 1 Enkephalin inhibition of atropine-resistant human detrusor contractions. Transmural electric field stimulation: 1 ms pulses, 10 Hz, 5 s train, field strength 0.15 kV/m.

In trigone, bladder neck and urethral strips, electrical stimulation can evoke both contraction and relaxation (Fig. 2). Stimulation with a frequency of 30 Hz will favour contraction and a frequency of 5 to 10 Hz will favour relaxation (Klarskov *et al.*, 1983). The relaxation was not affected by the enkephalins (n = 10, Fig. 3).

The enkephalins did not influence the tension or the spontaneous contractions of the strips. Contractions evoked pharmacologically with carbachol, noradrenaline, prostaglandin $F_{2\alpha}$ and substance P were also unaffected.

Strips stored for 24 h did not respond differently from those that were not stored.

Discussion

The present experiments demonstrated enkephalin inhibition of electrically evoked contractions on lower urinary tract smooth muscle. No influence was found on basal tension and rhythmic activity of the strips or on contractions evoked pharmacologically with carbachol, noradrenaline, prostaglandin $F_{2\alpha}$ and substance P. Therefore the inhibitory activity of the enkephalins must be presynaptic in nature. This inhibition was noted in similar experiments on smooth muscle from the oesophagus, stomach, jejunum, ileum and vas deferens (Waterfield *et al.*, 1977; Uddman *et al.*, 1980; Aleixandre *et al.*, 1981; Petkov and Radomirov, 1982). In colonic smooth muscle, enkepha-

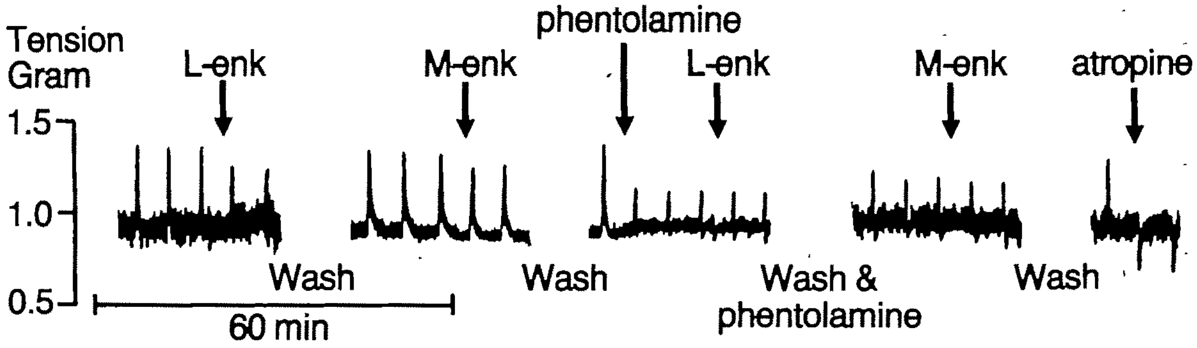

Fig. 2 Enkephalin inhibition of pig bladder neck contractions Transmural electric field stimulation· 1 ms pulses, 30 Hz, 5 s train, field strength 0.15 kV/m.

Table Enkephalin Inhibition of Electrically Evoked Contractions. Median Inhibition in Percentage with Ranges in 6 Experiments

	M-enk 0 1 μM		*L-enk 0 1 μM*	
	5-10 Hz	*30 Hz*	*5-10 Hz*	*30 Hz*
Human detrusor	21 (10-51)	15 (1-20)	12 (-2-38)	8 (1-14)
and phentolamine 4 μM	16 (2-24)	9 (3-14)	7 (3-14)	5 (3-8)
and atropine 0 4 μM	24 (7-50)	19 (7-21)	16 (10-18)	19 (12-33)
Pig detrusor	21 (14-44)	9 (7-16)	17 (8-19)	9 (5-15)
and phentolamine 4 μM	4 (0-18)	4 (0-7)	4 (-2-12)	2 (0-10)
and atropine 0 4 μM	17 (8-19)	7 (2-16)	14 (7-16)	7 (2-14)
Pig trigone, bladder neck				
and urethra		5 (2-18)		4 (3-25)
and phentolamine 4 μM		2 (0-17)		2 (-33-8)

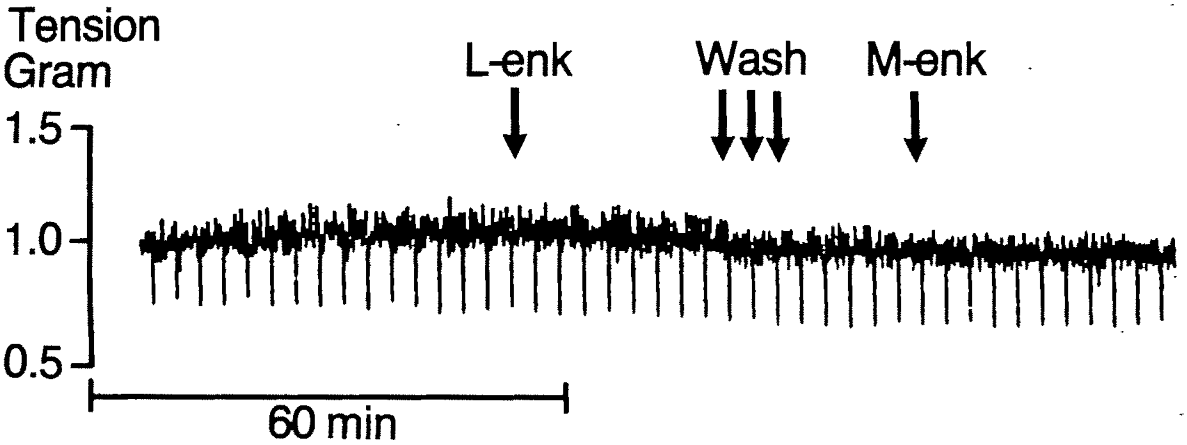

Fig. 3 Enkephalin and pig bladder neck relaxation Transmural electric field stimulation: 1 ms pulses, 5 Hz, 5 s train, field strength 0.5 kV/m The strip was blocked with atropine and ketoprofen 0 4 μM and phentolamine and propanolol 4 μM

lin seems to be excitatory (Hellström and Rosell, 1981; von Wienbeck and Dünzen, 1982). Presynaptic inhibition by enkephalins was also found in urinary bladder ganglia (Booth *et al.*, 1981; Simonds *et al.*, 1983), in cholinergic transmission in sympathetic ganglia (Konishi *et al.*, 1979), in the firing of single myenteric neurons (North *et al.*, 1979; Williams and North, 1979) and in the release of substance P from the trigeminal nucleus of the rat (Jessell and Iversen, 1977).

Contractions evoked by 30 Hz stimulation are more powerful than those induced by 5 to 10 Hz, but probably the latter frequency is more physiological. In accordance with this, the inhibition by enkephalin was more pronounced for contractions induced by 5 to 10 Hz than for contractions evoked by 30 Hz stimulation.

Phentolamine-resistant contractions were inhibited less by enkephalins than contractions that were not blocked and contractions resistant to atropine. This might indicate that contractions dependent on α-adrenergic transmission are more sensitive to the influence of enkephalin than contractions dependent on cholinergic transmission.

M-enk proved to be more potent than L-enk. M-enk and L-enk appear in different nerve populations (Larsson *et al.*, 1979). Neurons containing M-enk usually predominate, but differences do exist (Waterfield *et al.*, 1977; Iversen *et al.*, 1978; Vaalasti *et al.*, 1980; Miller, 1981). The distribution of M-enk and L-enk has not been clarified for the urinary tract.

The enkephalins did not mediate or antagonise the inhibitory nerve response of the trigone, bladder neck and urethral smooth muscle and the neuromuscular transmitter substance of this newly described response is still unknown (Klarskov *et al.*, 1983, 1984; Klarskov and Hørby-Petersen, 1986). This is in accordance with enkephalins being inactive in the relaxation response in colonic smooth muscle (Cocks and Burnstock 1979; Huizinga and Den Hertog, 1979).

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Eicosanoid Synthesis by Human Urinary Bladder Mucosa: Pathological Implications

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Summary—Biopsies of human urinary bladder mucosa obtained during cystoscopy were shown to release eicosanoids in the following order: prostacyclin (PGI_2), prostaglandin E_2 (PGE_2), prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) and thromboxane A_2 (TXA_2). The total and the relative amounts of eicosanoids released were similar to those reported for the rat urinary bladder. These eicosanoids may play a role in modulating the tone and contractility of the bladder as well as affecting cytoprotection of the mucosa. In view of the abundant release of eicosanoids by the bladder, caution must be exercised when considering urinary eicosanoid excretion as reflecting production by the systemic vasculature and/or the kidneys.

We have recently demonstrated that the urinary bladder of the rat synthesises prostacyclin (PGI_2), prostaglandin E_2 (PGE_2) and thromboxane A_2 (TXA_2). The *in vitro* synthesis of these eicosanoids was shown to be influenced by distension, pH and osmolarity (Jeremy *et al.*, 1984a), experimental diabetes mellitus (Jeremy *et al.*, 1986), cigarette smoke extracts and bladder carcinogens (Jeremy *et al.*, 1985a). These findings suggested two possible roles for urinary bladder eicosanoids:

(a) regulation of bladder smooth muscle activity

(b) cytoprotection of the urothelium. We proposed the latter function since it is well established that PGI_2 and PGE_2 have a cytoprotective action in various organs, such as the gastric and duodenal mucosa, where they probably exert their action through control of mucous secretion (Jeremy *et al.*, 1985a).

Since the urothelium possesses similar protective systems (Parsons *et al.*, 1980) and PGE_2 analogues have been successfully used to treat symptoms caused by schistosomal bladder ulcers and to stop bleeding due to cyclophosphamide-induced haemorrhagic cystitis (El Gendi *et al.*, 1982; Mohiuddin *et al.*, 1984), urothelial PGI_2 and PGE_2 production may play a role in protecting the bladder from irritation, ulceration and carcinogenesis. Since no data are available on the spontaneous release of eicosanoids by human bladder tissue, we investigated the synthesis of PGI_2, PGE_2, $PGF_{2\alpha}$ and TXA_2 using human mucosal biopsies obtained at diagnostic cystoscopy.

Materials and Methods

Mucosal biopsies were taken from consenting patients undergoing cystoscopy using the "pinch biopsy" technique (Storz biopsies 2 mm in diameter). Patients were undergoing cystoscopy for the investigation of:

(a) microscopic haematuria which was found not to be of bladder origin,

(b) benign prostatomegaly, or

(c) treated bladder neoplasms where at follow-up cystoscopy no evidence of recurrence was detected. The numbers of patients and smokers sampled in each group are shown in the Table. Smokers were arbitrarily defined as those currently and regularly smoking more than five cigarettes per day.

Mucosal biopsies for eicosanoid synthesis were taken from fundic sites with no overt pathology.

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The bladder was pre-irrigated with isotonic saline. The bladder pressure was not constantly monitored because of obvious technical difficulties in doing this However, all procedures were carried out with minimum bladder filling and therefore the intravesical pressure is unlikely to have exceeded 20 cm of water. The biopsies were washed in isotonic saline and stored at −70°C prior to eicosanoid analysis. The mucosal segments were placed in Dulbecco's Minimum Essential Medium (MEM; Gibco Biocult, Paisley) and incubated for 1 h, at 37°C, in a shaking water bath (Jeremy *et al*, 1984a). The incubation tubes were then centrifuged and an aliquot of the supernatant taken for estimation of 6-oxo-$PGF_{1\alpha}$ and TXB_2 (the stable hydrolysis products of PGI_2 and TXA_2 respectively), PGE_2 and $PGF_{2\alpha}$ by specific radioimmunoassay as previously described (Jeremy *et al.*, 1984a). Tissues were washed quickly in distilled water, desiccated and weighed.

Antisera of high serological specificity against 6-oxo-$PGF_{1\alpha}$, TXB_2, $PGF_{2\alpha}$ and PGE_2 were purchased from Capell Laboratories (West Chester, USA). ^3H 6-oxo-$PGF_{1\alpha}$, ^3H TXB_2, 3H PGE_2 and ^3H $PGF_{2\alpha}$, each with specific activities of 120 Ci/mmol were purchased from New England Nuclear (Dreieich, FRG). Unlabelled 6-oxo-$PGF_{1\alpha}$, TXB_2, PGE_2 and $PGF_{2\alpha}$ were purchased from Sigma Chemical Company (Poole). Radioimmunoassay procedures (buffers, equilibration conditions, charcoal separation of bound and unbound ligands) were carried out according to protocols obtained from Capell Laboratories. Validation of methods has been described in full elsewhere (Jeremy *et al.*, 1985b and c).

Results

Human bladder mucosal biopsies released substantial quantities of 6-oxo-$PGF_{1\alpha}$, PGE_2, $PGF_{2\alpha}$ and TXB_2 (Table). The order of quantitative predominance was: 6-oxo-$PGF_{1\alpha}$ $> PGE_2$ $\geqslant PGF_{2\alpha}$ $> TXB_2$.

There was a marked increase in PGI_2 release (assessed as 6-oxo-$PGF_{1\alpha}$) in the mucosal biopsies obtained from patients with benign prostatomegaly when compared with the other patient groups. Smoking did not appear to have a major effect on prostanoid release, but it is difficult to draw any conclusions because of the small numbers involved.

Table Prostanoid Release from Bladder Mucosal Biopsies (ng/mg dry weight tissue 1 h) (Results are expressed as median and (range))

	$PGF_{2\alpha}$	PGI_2	PGE_2	TXB_2
Group A—Microscopic haematuria—no bladder pathology n=7	1.3 (0.5-2.9)	20 (6-25)	2.7 (0.8-9.0)	1.1 (0.6-2.1)
Group B—Check cystoscopy Previous TCC n=5	2.4 (1.2-6.2)	21 (7-29)	2.3 (0.8-3.5)	0.9 (0.8-1.8)
Group C—Prostatomegaly n=5	*6.4 (4.1-9.6)	*58 (42-68)	4.6 (2.0-8.2)	1.3 (0.9-2.5)

Number of smokers. Group A n=2, B n=3, C n=2
Statistical analysis Mann Whitney test (two tailed)
* $P < 0.002$ Group A vs Group C

Discussion

The present preliminary findings demonstrate that human bladder mucosal biopsies synthesise substantial quantities of PGI_2 (measured as 6-oxo-$PGF_{1\alpha}$) and, to a lesser extent, $PGF_{2\alpha}$, PGE_2 and TXA_2 (measured as TXB_2). It would be reasonable to assume that the microscopic haematuria group with no detectable bladder pathology is the best approximation to the healthy control situation. It would therefore appear that benign prostatomegaly is associated with considerable enhancement of prostanoid release This finding is in agreement with our earlier observation that bladder distension (*in vitro*) and hypertrophic bladders in diabetic rats both result in enhanced eicosanoid release (Jeremy *et al.*, 1984a, 1986). Statistical analysis in the present communication must be interpreted with caution because of the small numbers involved and the lack of a clearly defined "normal" group. However, the message remains that human bladder tissue has the capacity to release spontaneously substantial amounts of eicosanoids and that this process may be altered in certain pathological states.

The relative amounts of the different eicosanoids produced by the human bladder mucosa were also of an order similar to those produced by the rat urinary bladder *in vitro* (Jeremy *et al.*, 1984a).

The findings of the present study are limited by the small numbers and by the fact that the amount of eicosanoids released may not be representative of the resting *in vivo* situation, since the trauma inherent in tissue preparation is a known stimulus of eicosanoid release (Jeremy *et al.*, 1984b). Furthermore, the small size of the mucosal biopsies used in the eicosanoid assay precluded their submission for histology. It was also felt that excessive manipulation of the biopsies would significantly alter spontaneous prostanoid release, since trauma initiates this process (Jeremy *et al.*, 1984b). Other mucosal biopsies collected from the same patients and submitted for histology revealed muscle layers in a few specimens. This latter observation therefore precludes an exact definition of the contribution of each layer to prostanoid synthesis. However, since all biopsies released substantial amounts of prostanoids, this study should be considered as evidence that the human urothelium can synthesise prostanoids. There is also evidence from animal experiments that both the urothelium and the bladder muscle layers have the capacity to release prostanoids (Brown *et al.*, 1980).

We previously suggested that certain prostanoids may play a cytoprotective role in the urinary bladder, acting in a manner similar to that shown in the human stomach (Konturek *et al.*, 1982; Yik *et al.*, 1982; Jeremy *et al.*, 1985c), and that diminished prostanoid synthesis may render the bladder susceptible to infection, ulceration and carcinogenesis (Jeremy *et al.*, 1985a). As in the gut, the mucosal surface secretes mucin, which protects the urothelium against the relatively hostile environment of urine (Parsons *et al.*, 1980). Whether eicosanoids are involved in maintaining the integrity of the urothelial glycosaminoglycan barrier is not known; however, in other tissues (Arumugham and Bose, 1982) the synthesis of glycosaminoglycans is inhibited by non-steroidal anti-inflammatory drugs, which are known inhibitors of prostaglandin synthesis. In this context, it is also of interest that glycosaminoglycans are thought to protect the urothelium from bacterial adhesion (Gill *et al.*, 1982) and that increased urinary excretion of PGE_2 has been reported in patients with acute bacterial cystitis (Farcas *et al.*, 1980).

The administration of PGI_2 and PGE_2 analogues also exerts beneficial effects on symptoms caused by schistosomal bladder ulcers and cyclophosphamide-induced haemorrhagic cystitis (El Gendi *et al.*, 1982; Mohiuddin *et al.*, 1984). It is of interest that both of these conditions, which were successfully treated with exogenous eicosanoids, are risk factors in the pathogenesis of bladder cancer (Fuchs *et al.*, 1981; Elem and Purohit, 1983) and that aspirin, which inhibits eicosanoid synthesis, can act as a co-carcinogen in certain animal models (Chang *et al.*, 1983). We have also demonstrated that cigarette smoke extracts and the carcinogen 2-naphthylamine are potent inhibitors of PGI_2 synthesis in the rat urinary bladder (Jeremy *et al.*, 1985a). Since cigarette smoking is a major risk factor in urinary bladder cancer (Morrison *et al.*, 1984), we suggested that smoking, through inhibition of cytoprotective eicosanoids, may play a role in the aetiology of bladder cancer (Jeremy *et al.*, 1985a). Unfortunately, the small numbers in the present study do not allow a definitive comment on the effect of smoking on bladder prostanoid production. We are, however, extending our patient population and carefully recording their smoking habits.

It is relevant to mention that not all prostanoids are cytoprotective: TXA_2 promotes ulcer formation (Whittle *et al.*, 1981) and enhances tumour growth in certain animal models (Honn and Meyer, 1981). However, we should also consider that the small amounts of TXA_2 we detected may have been generated by "activated" platelets trapped in the biopsy material.

The role of bladder prostanoids in maintaining tone and in initiating and sustaining voiding has been discussed elsewhere (Brown *et al.*, 1980; Jeremy *et al.*, 1984a and b).

The synthesis of substantial amounts of eicosanoids by the human bladder mucosa may have other implications, since urinary eicosanoid concentrations have been said to reflect changes in renal and systemic eicosanoid output in several pathological conditions in man (Jeremy *et al.*, 1984a). Since we have demonstrated, at least in the rat bladder, that pathological and metabolic variables (diabetes mellitus, pH, distension, osmolarity, cigarette smoke) markedly alter urinary bladder eicosanoid synthesis (Jeremy *et al.*, 1984a, 1985a, 1986), this assumption may no longer be valid. Therefore the potential contribution of bladder tissue to urinary eicosanoid levels must be considered in future studies.

Although the significance of the present study is limited by the small number of samples, it is hoped that these findings will encourage further research into the role of bladder prostanoids and their potential therapeutic applications.

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A Study of the Pathogenesis, Urodynamic Assessment and Outcome of Detrusor Instability Associated with Bladder Outflow Obstruction

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Summary—One hundred patients awaiting surgery for bladder outflow obstruction were studied prospectively. All patients completed a symptom score and had urodynamic studies pre-operatively. These results were not known to the urologist and did not therefore influence the course of surgery.

There was a good positive correlation between both the severity and the duration of irritative symptoms and the presence of detrusor instability. Eighty per cent of patients were significantly improved 3 months post-operatively. Patients with detrusor instability or low compliance were four times more likely to have an unsatisfactory outcome than those with stable bladders. The outcome could have been predicted in half of the unsuccessful patients on the basis of their pre-operative symptom score and urodynamic studies.

Whilst a full urodynamic evaluation is usually unnecessary, all patients should have a flow rate estimation and those with a high urgency symptom score and an unexpectedly high flow rate require full urodynamic assessment. These patients should be considered for alternative treatment or warned pre-operatively of the likely outcome.

There is still a remarkable lack of knowledge about the pathogenesis of detrusor instability in the presence of bladder outflow obstruction. The relative importance of age and the severity and duration of symptoms on the development of instability and their effect on the outcome after surgery remains uncertain.

The recognition of an association between bladder outflow obstruction and detrusor irritability is not new. John Hunter (1856) commented, "The disease of the bladder arising from obstruction alone, is increased irritability, and its consequences, by which it admits of little distension, becomes quick in its action and thick and strong in its coats." This was a clear reference to urgency and frequency of micturition.

Support for the association between bladder outflow obstruction and detrusor instability comes from the known high pre-operative incidence of instability in these patients and the fact that in most cases the instability resolves after relief of the obstruction (Table 1). More recently, however, it has been suggested that the instability is not due to the obstruction *per se*, but rather to the older age of these patients (Abrams, 1985). Therefore doubt remains about the nature of the correlation between bladder outflow obstruction and detrusor instability.

Fortunately, the overall surgical success rate is high, in the region of 70 to 90% (Abrams, 1977; Abrams *et al.*, 1979; Frimodt Moller *et al.*, 1984), but the remaining 10 to 30% of patients receive little benefit from surgery and it would be advantageous if we could predict this pre-operatively and offer alternative treatment. The value of urodynamic assessment, however, is still hotly debated (Abrams, 1978; Andersen, 1982; Frimodt Moller *et al.*, 1984) and although in some units it is routine practice, in the majority it is rarely undertaken.

Read at the Combined Meeting of the British Association of Urological Surgeons and the Canadian Urological Association in London, June 1986

Table 1 Incidence of Detrusor Instability before and after Prostatectomy

	Pre-operative		*Post-operative*	
Authors	%	*(n)*	%	*(n)*
Andersen (1976)	45	(94)	17	(21)
Abrams *et al.* (1979)	53	(100)	19	
Turner Warwick *et al.* (1979*)	71	(92)	38	
Price *et al* (1980)	73	(51)	—	
Andersen (1982)	53	(104)	14	(56)
Frimodt Moller *et al.* (1984)	65	(84)	22	(50)
Meyhoff *et al.* (1984)	80	(75)	51	(34)

(n) = Number of patients studied.
*Published in Abrams *et al.* (1979)

Table 2 Symptom Score—Urgency Section

Frequency (hours)	>3	0
	2–3	1
	1–2	2
	<1	3
Nocturia	0–1	0
	2–3	1
	3–4	2
	>4	3
Enuresis		1
Urgency	None	0
	Urgency alone	1
	Occasional incontinence	2
	Regular incontinence	3

The aims of this study were

(1) to correlate patient age, duration and severity of symptoms and the severity of obstruction with the presence of instability,

(2) to assess the importance of these factors on the outcome after surgery and

(3) to evaluate the role of urodynamics in the management of patients with bladder outflow obstruction.

Patients and Methods

A prospective study was carried out on consecutive patients who, on clinical and radiological grounds alone, were awaiting prostatectomy. All completed a detailed symptom score and had urodynamic studies immediately prior to surgery. Table 2 shows the urgency section of the symptom score. The obstructive symptoms of hesitancy, poor and intermittent stream and terminal dribbling were also recorded (Madsen and Iversen, 1983). A free flow rate estimation was followed by a standard supine and sitting cystometrogram and voiding study using a 10F filling catheter and a 4F pressure catheter. Abdominal pressure was measured as rectal pressure via a standard manometer line protected with a finger cot. The bladder was filled via a peristaltic pump at 50 ml/min with 0.9% saline. The results of these studies were not made available to the surgeon and did not, therefore, influence the decision to operate.

The presence of instability was taken as any inappropriate involuntary contraction resulting in a rise in subtracted detrusor pressure greater than 15 cm H_2O, during filling or on provocation when full. Any gradual rise in pressure during filling (>15 cm H_2O) was recorded as low compliance. Patients with chronic retention had their bladders filled after voiding and were not completely emptied until the end of the study.

All patients underwent cystoscopy followed by surgery to relieve their bladder outflow obstruction. They were reassessed 6 weeks and 3 months post-operatively with symptom scores. Repeat urodynamics were performed only on patients with an unsatisfactory outcome. Statistical analysis was performed using Student's *t* test.

Results

One hundred patients were studied. Their mean age was 68.5 years (range 52–83). Seventy patients were referred with symptoms of bladder outflow obstruction but without acute or chronic retention. Fourteen were found to have chronic retention and 16 presented with acute retention. The urodynamic studies revealed that 26 patients had detrusor instability, as previously defined, and 22 had low bladder compliance. Fifty-two had normal compliance and no instability and 25 of these showed evidence of bladder hypersensitivity. Thirteen of the patients with low compliance, including nine with chronic retention, had a reduction in compliance alone, and nine patients had a less marked rise in pressure, with superimposed small amplitude contractions (<15 cm H_2O). Patients with acute retention had a lower incidence of instability or low compliance (5/16).

Analysis of the urge section of the symptom score showed significant differences between the groups with detrusor instability (7.8 ± 1.1) or low compliance (7.2 ± 1.4) and those with stable bladders (3.9 ± 1.5) (mean ± SD) ($P < 0.001$) (Fig. 1). There was no statistical difference between the obstructive symptoms in the three urodynamic groups. In addition, there was no significant difference between the age of those patients with instability

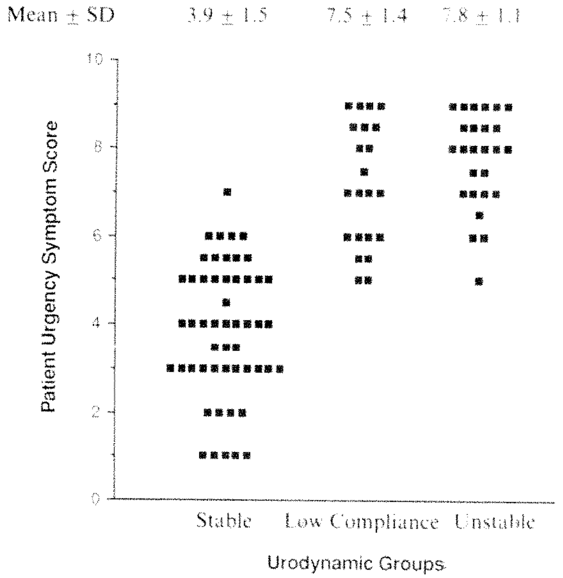

Fig. 1 Correlation of urgency symptom score with urodynamic findings.

(72 ± 6 years), low compliance (69 ± 7 years) or stable bladders (68 ± 6 years). However, symptom duration was 70% longer in the group with instability (4.8 years) than in those with stable bladders (2.8 years) ($P<0.05$). There was a good positive correlation between the incidence of instability and increasing symptom duration (Fig. 2). Eighty-four patients had transurethral prostatectomies, 10 had retropubic operations and six had bladder neck incisions. The mean prostatic weight was 29 g (range 3–112).

Three months post-operatively, 80 patients had a significant improvement in all symptoms with a reduction of more than 50% in their symptom scores. In particular, patients who presented with acute retention did well. Patients with detrusor instability or low compliance were four times more likely to have an inadequate reduction in their symptom score (16 patients) than those with stable obstructed bladders (4 patients). Whilst 92% of patients with stable bladders had a good result, only 52% of the group with instability had a satisfactory outcome (Fig. 3). Those patients with an unexpectedly high flow rate and the presence of instability did less well. However, the severity of obstruction overall, measured as the urethral resistance factor (P/F^2), did not correlate well with the presence of instability or the outcome after surgery.

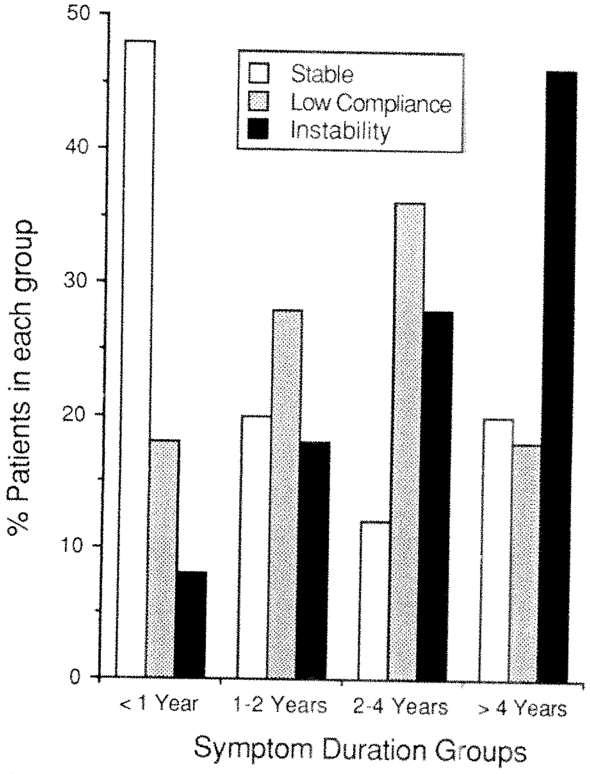

Fig. 2 Comparison of duration of symptoms with urodynamic findings.

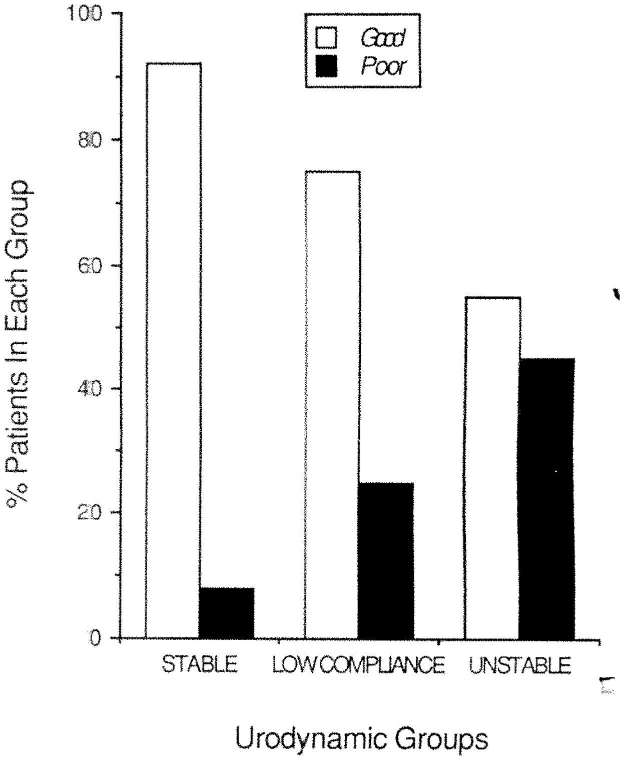

Fig. 3 Correlation of urodynamic findings with subjective results 3 months post-operatively.

There was no correlation between prostatic weight or the operation performed and either the presence of instability or the outcome after surgery.

Discussion

Detrusor instability was present in 26 patients in this study and a further 22 had low compliance. This is a combined incidence of 48%. Analysis of published series (Table 1) shows that the pre-operative incidence of instability varies from 45 to 80%. However, this variation is probably due to differences in patient recruitment and urodynamic technique between the various studies. For example, Price *et al.* (1980) studied only patients with both obstructive *and* urgency symptoms and Turner-Warwick *et al.* (1979) (see Abrams *et al.*, 1979) filled their patients' bladders at 150 ml/min—a rate 3 times faster than in the majority of studies. Meyhoff *et al.* (1984) also used rapid fill urodynamics via a catheter with a balloon inflated on the trigone. All of these factors would serve to increase the incidence of pre-operative instability or low compliance. The true pre-operative incidence is probably in the region of 50%, and in half to two-thirds of these patients the urodynamic studies return to normal post-operatively. The lower than expected incidence of instability in this series may be partly due to the fact that patients with marked irritability (and instability) were selected out because they underestimated their outflow problems. A flow rate alone would show up this group of patients. Stratification of our patients without those who presented with acute or chronic retention has the effect of increasing the incidence of instability and decreasing that of low compliance. The long-term outcome of our patients with unsatisfactory results is not yet known, but resolution of instability is possible 6 or even 12 months post-operatively (Price *et al.*, 1980; Frimodt Moller *et al.*, 1984) and in some of the remaining patients there may be persistent obstruction that may be relieved by further surgery (Turner-Warwick *et al.*, 1973). However, 11 of the 20 patients who had a poor post-operative result could have been predicted pre-operatively, on the basis of an unexpectedly high flow rate, normal voiding pressures and the presence of instability. All of these patients had an urgency symptom score greater than 5.5.

Unlike Rao *et al.* (1979), we agree with Dorflinger *et al.* (1985) that the presence of instability pre-operatively is associated with a greater likelihood of unacceptable symptoms post-operatively. Unlike the latter authors, however, we feel that there is a role for pre-operative urodynamics in patients with bladder outflow obstruction. We suggest that whilst routine urodynamic studies in all patients with bladder outflow obstruction add little to their management, all patients should have a flow rate estimation and any patients with a high urgency symptom score (>5.5) and an unexpectedly high flow rate (>12 ml/s) need full urodynamic studies. This represented 11% of the patients in this series and the majority of these patients would, in future, not require surgery in the first instance. In addition, using these same criteria it is possible to predict which patients are likely to have a less satisfactory result with surgery and they could be warned accordingly.

Once again the association between bladder outflow obstruction and detrusor instability has been demonstrated. There is a good correlation between the severity and duration of symptoms and the presence of instability. This would seem to indicate that a higher priority for prostatectomy should be given to patients with a longer duration of symptoms and those with marked irritative symptoms and a poor flow rate. We found no association between increasing age and either the incidence of instability or the possibility of a poor post-operative outcome; there was no correlation between the severity of obstruction (P/F^2) and the presence of instability. However, it is unlikely that the severity of obstruction is unimportant, rather that the patients with more severe obstruction present earlier and do not therefore develop the later sequelae of outflow obstruction, such as instability and decompensation.

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Changes in Urodynamic Measurements after Successful Anal Electrostimulation in Female Urinary Incontinence

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Summary—Fifty-five of 71 women with stress, motor urge and mixed stress and motor urge urinary incontinence were treated successfully with a new integrated electrostimulation device (Incontan) used anally. Changes in urodynamic measurements were evaluated when the patients themselves reported cure or significant improvement. The duration of the treatment was 9 to 20 h/day for at least 2 months (mean 9 months). According to the patients' subjective evaluation, 71% were cured of their incontinence and 29% were markedly improved.

In motor urge and mixed incontinence a significant increase in bladder volume at first sensation and at maximum cystometric capacity was found, and 45% of these patients had a normal, stable bladder after treatment. A significant increase in functional urethral length was observed in patients who had had stress incontinence, but the measured increase in maximum urethral pressure was not significant. Of the 16 patients with stress and mixed incontinence who reported cure, 15 had a positive urethral closure pressure during coughing after treatment. Urodynamic analysis confirmed the positive clinical effect observed after electrostimulation therapy. It is recommended as primary therapy in stress, motor urge and mixed stress and motor urge incontinence in women.

Contractions of the pelvic floor muscles can be obtained by electrical stimulation using intramuscular electrodes, direct nerve stimulation or reflex stimulation from vaginal or anal stimulators. Reflex stimulation is most effective, activating a number of muscles from a single stimulation site. In addition, it requires a minimum amount of stimulation intensity. Anal seems to be more effective than vaginal stimulation (Racovec, 1976).

During pelvic floor stimulation, detrusor activity is inhibited via two spinal reflex pathways which can operate without supraspinal control (Fall *et al.*, 1977). These pathways are activated by stimulation of pudendal nerve afferents, after which activation of pudendal and hypogastric nerve efferents will cause a contraction of smooth and striated urethral muscles and striated pelvic floor muscles.

A new electronic device for anal electrical stimulation (Incontan) has been developed (Bergmann and Eriksen, 1986) and a clinical evaluation of its effect on female urinary incontinence was reported by Eriksen *et al.* (1986). The purpose of the present study was to compare the urodynamic measurements before and after successful treatment with Incontan in women with stress incontinence, motor urge incontinence and mixed stress and motor urge incontinence, to see if the clinical results could be verified by objective urodynamic measurements.

Patients and Methods

From the patients with urinary incontinence seen in the out-patient clinic of the Department of Obstetrics and Gynaecology, 71 women were

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Table 1 Type of Incontinence based on Urodynamic Evaluation before Treatment

	No. of patients			
	Selected for treatment	*Unable to use the stimulator*	*No effect*	*Study group Cured/improved*
Stress	31	3	2	26
Stress/motor urge	20	4	3	13
Motor urge	19	2	2	15
Sensory urge	1	—	—	1
Total	71	9	7	55

selected for treatment with Incontan (Table 1). The diagnosis for each patient was established from a general case history, detailed inquiry concerning lower urinary tract function, residual urine measurements, a stress test, simultaneous cystoflowmetry and measurement of the urethral pressure profile. The degree of incontinence was assessed from the patient's medical history and micturition charts. The complete evaluation included urine culture, gynaecological examination, examination of sacral reflex activity and sensitivity in the same area and cystourethroscopy. Nine patients were unable to use the stimulator and stopped treatment within 2 months. Three of them were unable to co-operate because of senile dementia, two felt the treatment aesthetically unacceptable, three stopped treatment because of anal pain and one experienced increasing sciatic pain after an operation for a prolapsed disc. Seven patients used the stimulator as recommended with little or no effect. The study group thus consisted of 55 women with urinary incontinence who were successfully treated by electrostimulation.

Urodynamic procedure

Initially, flowmetry was recorded during spontaneous micturition. Residual urine was measured through a 12 F Foley catheter inserted transurethrally to the bladder together with a 5 F Portex catheter for intravesical pressure registration via a strain gauge transducer AE 840 at the level of the symphysis. Intra-abdominal pressure was recorded rectally. The pressure measurements were transmitted to a 6-channel Mingograph 830 ink jet recorder (Siemens). Detrusor pressure was derived by subtracting the intra-abdominal pressure from the intravesical pressure. A cystometrogram was performed with the patient in a sitting position to record maximum cystometric capacity, sensory function and stability. Cystometry was performed using 0.9% saline solution at body temperature with a filling rate of 25 ml/min. Finally, the 12 F catheter was removed, a simultaneous pressure/flow examination was made and the urethral resistance index calculated.

The bladder was then filled with 200 ml saline solution and three urethral pressure profiles were measured using a Millar microtip transducer (Texas Instruments) PC 771 size 7 according to the technique described by Asmussen and Ulmsten (1976). The catheter was withdrawn at a constant speed of 2.5 mm/s with the transducer in the 12 o'clock position using a motor driven mobile steering arm (Vingmed UP 20). Maximum urethral closure pressure and functional profile length were obtained during rest and vigorous coughing. All patients had sterile urine before the urodynamic study. Urethrocystoscopy revealed no bladder anomalies such as tumours, stones or diverticula.

After electrostimulation therapy had started, the urodynamic study was repeated when cure was reported by the patient, or after 1 or 2 years as part of the follow-up of those who claimed to have improved significantly during treatment.

Treatment lasted for at least 2 months, the stimulator being used 6 to 20 h/day, depending on the individual, for 2 to 36 months (mean 9). The patients' ages ranged from 30 to 80 years (mean 54) and the duration of incontinence varied between 1 and 40 years (mean 12). During the period of electrical stimulation all other treatment for incontinence was discontinued. About 30% of the patients had undergone one or more unsuccessful operations for incontinence. Drug treatment had also been tried unsuccessfully.

Methods, definitions and units conform to the standards proposed by the International Continence Society. The statistical method employed was Student's t test (5% level of significance).

Results

Based on a clinical evaluation of the 62 women who used the stimulator for at least 2 months, 39 (63%) were cured of incontinence; 16 (26%) were markedly improved and reported a normal social situation. Only seven patients (11%) reported little or no effect (Eriksen and Bergmann, 1986).

The cystometric findings in the 55 successfully treated patients are presented in Table 2. There was an increase in bladder volume measured at first sensation and at maximum cystometric capacity. The maximum detrusor contraction pressure observed in motor urge and mixed urinary inconti-

Table 2 Cystometric Findings before and after Successful Electrostimulation in 55 Patients

	Before treatment *Mean ± SD*	*After treatment* *Mean ± SD*	*P*
First sensation	105 ± 87 ml	149 ± 97 ml	<0.005
Maximum cystometric capacity	319 ± 110 ml	370 ± 127 ml	<0.05
Maximum detrusor pressure	53 ± 37 cm H_2O	42 ± 30 cm H_2O	<0.05
Residual urine	10 ± 16 ml	5 ± 13 ml	<0.05

Table 3 Cystometric Findings before and after Successful Electrostimulation in 29 Women with Motor Urge, Sensory Urge or Mixed Motor Urge and Stress Incontinence

	Before treatment *Mean ± SD*	*After treatment* *Mean ± SD*	*P*
First sensation	72 ± 47 ml	132 ± 93 ml	<0.001
Maximum cystometric capacity	282 ± 85 ml	358 ± 132 ml	<0.05
Volume threshold for detrusor contraction	183 ± 133 ml	286 ± 179 ml	<0.005
Maximum detrusor contraction pressure	62 ± 38 cm H_2O	49 ± 28 cm H_2O	<0.05

Table 4 Urethral Pressure Profile before and after Successful Electrostimulation in 34 Women with Stress and Mixed Stress and Urge Incontinence

	Before treatment *Mean ± SD*	*After treatment* *Mean ± SD*	*Significance*
Functional profile length	31.2 ± 6.3 mm	34.7 ± 6.2 mm	*
Maximum urethral closure pressure	44.8 ± 13.0 cm H_2O	45.9 ± 15.7 cm H_2O	NS

* $P < 0.001$

nence was reduced, but there was no increase in residual volume during treatment.

The patients with genuine stress incontinence had a stable bladder with normal capacity before and after therapy and no significant changes were observed in the cystometrograms in this subgroup In patients with an unstable bladder or sensory urgency, the changes in the cystometric measurements were even more pronounced and statistically significant (Table 3). The volume threshold for first desire to void and for uninhibited detrusor contractions increased in the improved patients. Thirteen patients (45%) with an unstable bladder before treatment had a stable bladder afterwards, with normal cystometric capacity.

Table 4 shows the changes in the urethral closure pressure profile after treatment in patients with stress and mixed incontinence. There was a significant increase in functional profile length, but the increase in maximum closure pressure was not significant. In the same group during vigorous coughing it was found that the closure pressure changed from negative to positive in 71% of patients after treatment (Table 5). In the 16 patients with stress and mixed urinary incontinence who reported cure, 94% had a positive closure pressure during coughing (Table 6). Maximum urethral closure pressure was measured with the patient in the supine position. Before treatment 65% had visible leakage while coughing; after treatment this was reduced to 18%.

Twenty-one patients (38%) were subjectively cured and their urodynamic measurements returned to normal. No significant change in the urethral resistance index was found.

The average peak flow rate was 24.0 ml/s before and 27.8 ml/s after treatment. The average flow time was reduced from 30.4 s to 28.5 s. There were no problems with bladder emptying either during or after treatment.

Discussion

These urodynamic results confirm the positive therapeutic effect of pelvic floor stimulation observed clinically in women with motor urge,

Table 5 Maximum Urethral Closure Pressure during Coughing in 34 Patients with Stress or Mixed Urinary Incontinence after Successful electrostimulation

	Maximum urethral closure pressure		
Type of incontinence	*Before treatment* *Negative*	*After treatment* *Positive*	*Negative*
Stress	20	14	6
Stress and motor urge	14	10	4
Total	34	24	10

Table 6 Maximum Urethral Closure Pressure during Coughing in 16 Patients Cured of Stress or Mixed Urinary Incontinence

	Maximum urethral closure pressure		
Type of incontinence	*Before treatment* *Negative*	*After treatment* *Positive*	*Negative*
Stress	11	10	1
Stress and motor urge	5	5	—
Total	16	15	1

stress and mixed urinary incontinence (Eriksen *et al.*, 1986).

The detrusor relaxation induced by electrostimulation increased bladder volume both at first desire to void and at maximum cystometric capacity. Forty-five per cent of patients with a hyperactive detrusor had a stable bladder after treatment. We also found a reduced isometric detrusor contraction and a reduction in micturition pressure without subsequent voiding problems, since there was no reduction in peak flow rate or voiding time. These results are similar to those of Godec *et al.* (1975), Fall *et al.* (1977), Godec and Cass (1980) and Laval (1983) and confirm that detrusor hyperactivity is permanently inhibited by electrical stimulation (Fall, 1984). The inhibition is claimed to be most effective between 5 and 10 Hz (Fall *et al.*, 1977) but we obtained excellent detrusor relaxation with a fixed frequency of 25 Hz.

The therapeutic effect in cases of stress and mixed incontinence may be explained by the significant increase in functional urethral length, even if no significant increase in maximum urethral closure pressure was recorded. An increase in urethral length unaccompanied by changes in urethral profile height has been recorded by Harrison and Paterson (1970) and Harrison and Constable (1970). Alexander and Rowan (1970) showed that such lengthening occurred on voiding cystourethrograms during electrostimulation using anal plug electrodes. They also found an increase in the urethral resistance index. Others have found an increase in urethral pressure of 30 to 40% during anal and vaginal stimulation in women with stress incontinence (Racovec, 1976). However, Edwards and Malvern (1972) stated that successful treatment of stress incontinence by electrostimulation could not be correlated to an improvement in sphincter resistance as measured by the urethral pressure profile.

What detailed mechanisms are responsible for the beneficial effect of pelvic floor stimulation in patients with urinary incontinence?

Janez *et al.* (1981) found that anal sphincter stimulation in rabbits produced increased beta-adrenergic activity in the detrusor muscle, while the activity of cholinergic receptors was decreased. Further studies are necessary before conclusions can be drawn about the nature of these changes and whether they are due to an increased number of receptors or an altered affinity to the receptors. A permanent change in beta-adrenergic activity can explain why motor urge incontinence seems to be cured in some patients (Fall, 1984).

An additional effect of bladder inhibition is the tightening of the detrusor sling fibres at the bladder neck (Tanagho and Smith, 1968). This is important in maintaining the passive continence which is lacking in women with stress incontinence and may partly explain the successful effect of electrostimulation in stress and mixed incontinence. Lapides (1958, 1965) stressed the significance of urethral length in the maintenance of continence. When intra-anal stimulation is applied, the impulses are transmitted to the external anal sphincter, the puborectalis muscle and the muscular urogenital diaphragm and produce sustained muscle contraction, elevation of the bladder base and elongation of the urethra. This increases the tension of the urethral wall, decreases the radius of the urethra and increases the outflow resistance (Sotiropoulos, 1975). Furthermore, lengthening of the urethra and bladder neck will normalise the intra-abdominal pressure transmission to the proximal urethra (Enhørning, 1961). Koinuma *et al.* (1981) applied efferent bilateral pelvic nerve stimulation to dogs; they observed a rise in intraluminal urethral pressure, a prolongation of the longitudinal axis and shortening of the transverse axis at all points of the urethra.

The effect of incontinence surgery has been described as tightening of the pubovesical fascia, thereby limiting urethral mobility under physical stress. Elevation of the bladder neck to its normal position will improve pressure transmission to the proximal third of the urethra and increase urethral resistance. The same factors are involved during electrostimulation, which probably represents a more physiological form of treatment of pelvic floor weakness. A higher success rate after electrical stimulation might be expected in patients without previous surgery for stress incontinence (Harrison and Paterson, 1970).

Finally, we found good correlation between the results based on clinical evaluation and those obtained from urodynamic examination. Our experience is that when the patient says she is continent, we can expect normal urodynamic findings.

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Urodynamic Findings in Sacrococcygeal Chordoma

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Summary—The clinical and urodynamic findings in two cases of sacrococcygeal chordoma are described. The urodynamic findings suggest that the urinary problems in this condition are caused by an incomplete lower motor neurone lesion.

Chordomas are rare malignant tumours which are believed to arise from remnants of notochord along the cerebrospinal axis. The anatomical distribution of the tumour is approximately 41% sacrococcygeal, 41% spheno-occipital and 18% vertebral (Beaugié *et al.*, 1969).

Chordomas are slow growing and have a poor prognosis, depending on local spread to bone and soft tissue. The prognosis improves with early diagnosis. Distant metastases are uncommon and occur late in the disease, more commonly in sacrococcygeal chordomas. These tumours are often missed, the diagnosis being long delayed. Gross (1983) related this to a low index of suspicion on the part of the doctor and also to problems in obtaining adequate X-rays.

The most frequent presenting symptom is pain in the lower back, buttocks or perineum. Constipation and incontinence of urine also occur but less commonly (MacCarty *et al.*, 1975). Such patients sometimes have a presacral tumour mass which can be felt on rectal examination.

Two cases of sacrococcygeal chordoma are reported in which the patients presented with incontinence of urine. We believe this is the first report of specific urodynamic findings in this condition and we suggest that these findings may be a useful diagnostic aid in certain cases.

Patients

Case 1

An 86-year-old woman was referred in February 1984 with a 5-month history of incontinence of urine. She was wet by day (× 4–5) and night (× 3); there was no warning, urgency or dysuria. Standing or bending precipitated incontinence. Her stream was poor and she felt she emptied her bladder completely. She was constipated and complained of vague perineal pain. She was taking imipramine for incontinence without benefit.

Eight years earlier she had presented to the gynaecologist with a 3-month history of frequency of micturition, constipation and pain in the right buttock. She had a moderately sized cystocele and a large rectocele, both of which were repaired. She apparently remained well until the onset of the presenting problem.

Examination was normal except for constipation. Routine investigations (SMAC profile, FBC, chest X-ray) were normal. There was a urinary tract infection which was treated. The constipation was relieved with a purgative. Imipramine was stopped. Urodynamic assessment (Abrams *et al.*, 1983) revealed a maximum flow rate of 5 ml/s, the volume voided being 100 ml. The bladder was filled from empty to a volume of 590 ml when incontinence occurred. There was a steady rise in subtracted detrusor pressure during filling (rate 50 ml/s) to a maximum of 22 cm H_2O (Fig. 1). There was an initial residual volume (after voiding) of 300 ml. The urethral closure pressure was 0 cm H_2O. An IVU performed 2½ weeks later showed a "very large residual volume". No obvious cause of bladder neck obstruction was found. She was unable to master self-catherisation and a permanent indwelling catheter was inserted. At follow-up in October 1984, her main problems were constipation requiring manual evacuation and lower back pain which radiated to her left leg. Rectal examination revealed

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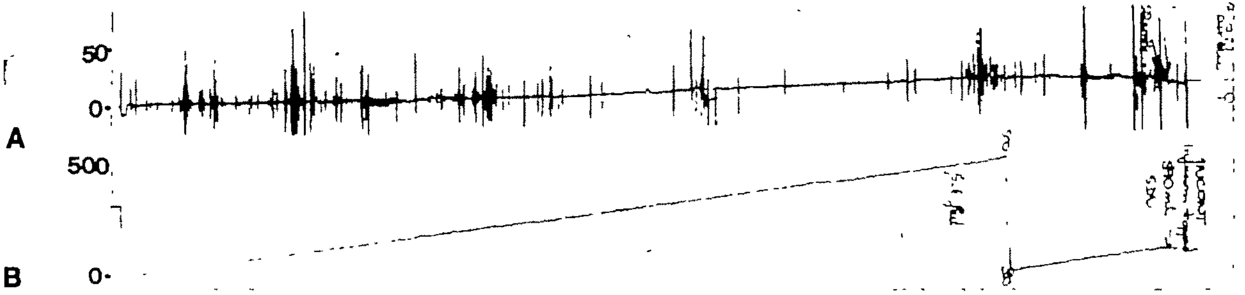

Fig. 1 (A) Case 1 Subtracted detrusor pressure (cm/H_2O) (B) Infused volume (ml)

a smooth hard mass posteriorly. X-ray of the lumbar spine was normal but the sacrum was not clearly visualised.

One month later she died suddenly. Post mortem revealed massive left cerebral infarction and sacrococcygeal chordoma.

Case 2

A 68-year-old woman presented in February 1985 with a 10-month history of back pain. The pain was intermittent, situated at the base of the back and over recent months had started to radiate to the back of both legs. Some relief was obtained by walking. External rotation of the right leg caused shooting pains in that limb. For 9 months before presentation she had had episodes of numbness affecting the perineum and feet, the former being occasionally associated with feelings of sexual arousal. She had been constipated for 3 weeks and incontinent of urine for 1 week before presentation. She was wet by day (×10–12) and night (×2). There was no warning or urgency. Incontinence was precipitated by standing. Her stream was "a trickle" and she felt her bladder was empty after micturition.

The only persistent abnormal finding on examination of the CNS was absent ankle jerks. Other systems were normal. Routine investigations were normal (SMAC, FBC, PV, glucose MSSU). X-ray of the chest and lumbosacral spine, myelogram and CT body scan were all normal.

Incontinence of urine remained a problem and the patient was referred for urodynamic assessment (Abrams *et al.*, 1983). The maximum flow rate was 20 ml/s and the volume voided was 250 ml. The bladder was filled after emptying to a capacity of 640 ml before incontinence occurred. There was a steady rise in subtracted detrusor pressure during filling (rate 50 ml/s) to a maximum pressure of 26 cm H_2O (Fig. 2). The initial residual volume (after voiding) was 250 ml. The urethral closure pressure was 10 cm H_2O. She was noted to have faecal retention.

The patient was treated with intermittent self-catheterisation and mannitol for constipation with some success initially. However, the constipation remained a problem and her pain became severe, requiring morphine to relieve it. A further X-ray of the lumbosacral spine showed an expanding lesion in the sacrum and review of the CT body scan showed a mass starting in the body of SI and descending as a soft tissue mass to the level S3–4. Needle biopsy of this lesion showed the histological appearances of a chordoma. It was felt that surgery was not indicated and the patient is receiving radiotherapy in an attempt to control her pain.

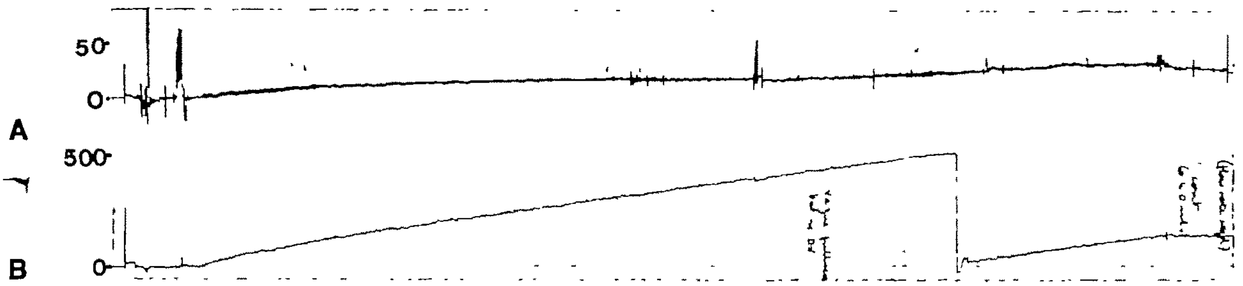

Fig. 2 (A) Case 2 Subtracted detrusor pressure (cm/H_2O). (B) Infused volume (ml)

Discussion

One year separated the presentation of these two patients and during this time 94 women underwent urodynamic assessment. One other woman, with urodynamic findings similar to those of the patients described, complained of constipation but not low back pain. No definite diagnosis was made and she died at home. In the literature concerning this condition urinary problems are variously described, *e.g.* urinary retention (Gray *et al.*, 1975), frequency, urgency and difficulty in starting the urinary stream (Mindell, 1981) and stress incontinence (Voight and Kenefick, 1971). No urodynamic findings are reported in these studies.

Several hypotheses have been suggested to explain the urinary problems which occur in sacrococcygeal chordoma. In 1975 MacCarty *et al.* stated that incontinence of urine developed because of bilateral involvement of second, third and fourth sacral nerves. Gray *et al.* (1975) proposed that antesacral tumours may directly obstruct the bladder, resulting in dysuria, frequency and urinary retention. In 1981 Mindell suggested that nerve dysfunction may cause urinary incontinence. The lower urinary tract urodynamic findings were similar in both of our patients. Bladder capacity was high. Detrusor activity slowly increased to a maximum pressure above normal (with no isolated detrusor contractions). Compliance was low (<35 ml/cm H_2O). The flow rate was reduced. Voiding was voluntary but there was a large residual volume. Sensation was reduced.

The findings are compatible with an incomplete lower motor neurone lesion and we suggest that tumour involvement of sacral nerve roots is the cause of this.

Such a urodynamic picture is unusual in women (3.2% of women in 1 year in this unit) and we propose that should it occur, a diagnosis of sacrococcygeal chordoma should be considered, even though further information on the urodynamics of this condition is needed.

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Urinary Fibrin/Fibrinogen Degradation Products in Transitional Cell Carcinoma of the Bladder

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Summary—Urinary fibrin/fibrinogen degradation products (FDPs) were measured in 210 specimens from 174 patients with newly or previously diagnosed transitional cell carcinoma of the bladder. They were detected in 94% of patients with deeply invasive bladder tumours (pT2–4) compared with 17% of superficial tumours. Microalbuminuria (>50 µg/g creatinine) was also found in 80% of patients with pT2–4 lesions. Both were compared with urine cytology.

Urinary FDPs are markers of bladder tumour invasion. Our results suggest that urinary FDPs are not of value in screening for the presence of bladder neoplasia but their role may be in following patients with superficial bladder tumours to detect those tumours which become invasive. The mode of excretion of the FDPs in the urine is discussed.

Regular check cystoscopy remains the standard method of follow-up of patients with transitional cell carcinoma of the bladder.

Urine cytology has proved a useful adjunct but not a substitute for cystoscopy in the management of bladder neoplasia. It is of limited value in low grade tumours, with a false negative rate of up to 74% (El Bolkainy, 1980). With the more invasive and higher grades of tumour, cytology nearly always gives a positive result (de Voogt and Wielenga, 1972). Cytology becomes positive in 80% of patients who later develop recurrent tumour but it is not a prognostic factor. Results do not differ between patients who develop progressive recurrent tumours and those who develop recurrent tumours that do not progress (Huland *et al.*, 1983). Cytology correlated with cystoscopic findings in 77% of bladder tumour patients (Dubernard *et al.*, 1982). Negative cytology was found in 98% of controls and 94% of bladder tumour patients with negative cystoscopies. However, only 36% of positive cystoscopies in the same series were identified by cytology (Dubernard *et al.*, 1982).

Wajsman *et al.* (1975) studied urinary FDPs in 66 patients with bladder tumours. They found that the correlation between the presence of FDP and activity of disease was 72%. By adding FDP positivity to cytology positivity the accuracy rate was increased to 90%. The clinical stages and grades of tumour were not analysed. In a further study by Wajsman *et al.* (1978) the urinary FDPs were elevated in only 32% of patients with a bladder tumour and cytology was positive in 71%, but 80% had positive urinary FDPs or positive urinary cytology or both. When both FDP and cytology were positive, an active tumour was present in 90% of cases.

Yu (1983) showed in an analysis of 200 specimens that only 8% of superficial tumours had raised urinary FDPs; elevated levels were found in 71% of advanced bladder tumours (pT2–pT4). He also found the mean concentration of urinary FDPs to be much higher in advanced bladder tumours than in superficial lesions.

In 1984 Jayachandran *et al.* showed the relationship of urinary FDPs to tumour stage. All high grade invasive tumours had FDPs elevated above 5 µg/ml (mean 53). Of 42 patients with previous bladder tumours and negative cystoscopy only one had a positive result. The FDP and cytology results had a high correlation.

More recently, McCabe *et al.* (1984) used a

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monoclonal antibody assay to show a 75% accuracy rate for FDPs in determining the current status of bladder tumour patients.

Raised urinary FDPs have been found in renal transplant rejection (Clarkson *et al.*, 1970), in glomerulonephritis (Clarkson *et al.*, 1971) and in upper urinary tract infections (Whitworth *et al.*, 1973). Jayachandran *et al.* (1984) found raised levels in seven of nine patients with renal stones. Lower urinary tract infections are not associated with elevated FDPs (McCabe *et al.*, 1984).

There have been several reports of urinary protein excretion in patients with bladder tumours (Johansson, 1975; Johansson and Kistner, 1975; Hemmingsen *et al.*, 1981). Hemmingsen *et al.* (1981) observed increased excretion of high molecular weight proteins and albumin in patients with advanced bladder tumours. The predictive value of a positive and negative result was 92 and 100% respectively. It was of no value in superficial tumours.

Patients and Methods

A prospective study was made of 174 patients (130 males and 44 females) with bladder cancer (145 had a previously diagnosed and treated lesion and 29 presented with a newly diagnosed transitional cell carcinoma). Their ages ranged from 42 to 86 years (mean 68.3). Thirty-two patients were examined on two occasions and two patients on three occasions. In all, 210 urine samples were examined.

Urine samples were collected for FDP estimation (210 specimens), for cytology (183), for microscopy and culture (209) and for albumin measurement (204). Cystoscopy was then performed on all patients; if a tumour was found, it was biopsied to obtain histological grading and staging. All tumours were classified according to the TNM classification (UICC, 1978).

A control group of 35 patients was also studied. Their ages ranged from 21 to 82 years (mean 62.7). Their diagnoses included benign prostatic hypertrophy (15 patients), carcinoma of the prostate (3), renal stones (5), previous haematuria (6), previous infective conditions (5) and urethral stricture (1). Patients with macroscopic haematuria were not entered into the study.

The FDPs were measured by a haemagglutination inhibition method (Merskey *et al.*, 1966), using a kit obtained from Wellcome Diagnostics, Beckenham. The test was consistently sensitive to 1.25 μg/ml and often sensitive to 0.6 μg/ml (the maximum sensitivity of the kit).

The albumin was measured by single radial immunodiffusion using antisera and standards provided by Behringwerke, Marburg, FDR. The levels of albumin and FDPs were corrected for urinary creatinine concentration and expressed as μg/g creatinine.

Results

The patients with previously or newly diagnosed transitional cell carcinoma of the bladder were divided into groups A to E, according to the findings at cystoscopy (Group A = clear cystoscopy; B = pTa; C = pTis; D = pT1; E = pT2–4). Group F was the control group.

Table 1 shows the number and percentage of patients in each group with detectable FDPs in their urine. Group E (pT2–4) had the highest percentage of positive urinary FDPs (93.9%); this was significantly higher than groups A to D individually and together ($P<0.001$; standard χ^2 test). Excluding group E, none of the other groups reached statistical significance when compared with each other ($P>0.5$; standard χ^2 test). The mean values of FDPs in each group are also shown in Table 1 and the exact values in Figure 1. Analysing the elevated values of FDP in each group, group E (pT2–4) had significantly higher elevated FDP values than the equivalent elevated values for the other groups combined ($P<0.025$; non-parametric Kruskal-Wallis test).

The results for the albumin estimations are

Table 1 Urinary FDPs in Patients with Transitional Cell Carcinoma and Controls

Group	*Histology*	*Specimens examined*	*Specimens with detected FDPs*	*% Detected*	*Mean value FDPs μg/g creatinine*
A	Clear	61	10	16.4	2.18
B	pTa	47	5	10.6	0.65
C	pTis	10	2	20.0	0.92
D	pT1	59	11	18.6	1.50
E	pT2–4	33	31	93.9	74.70
F	Controls	35	4	11.4	0.34

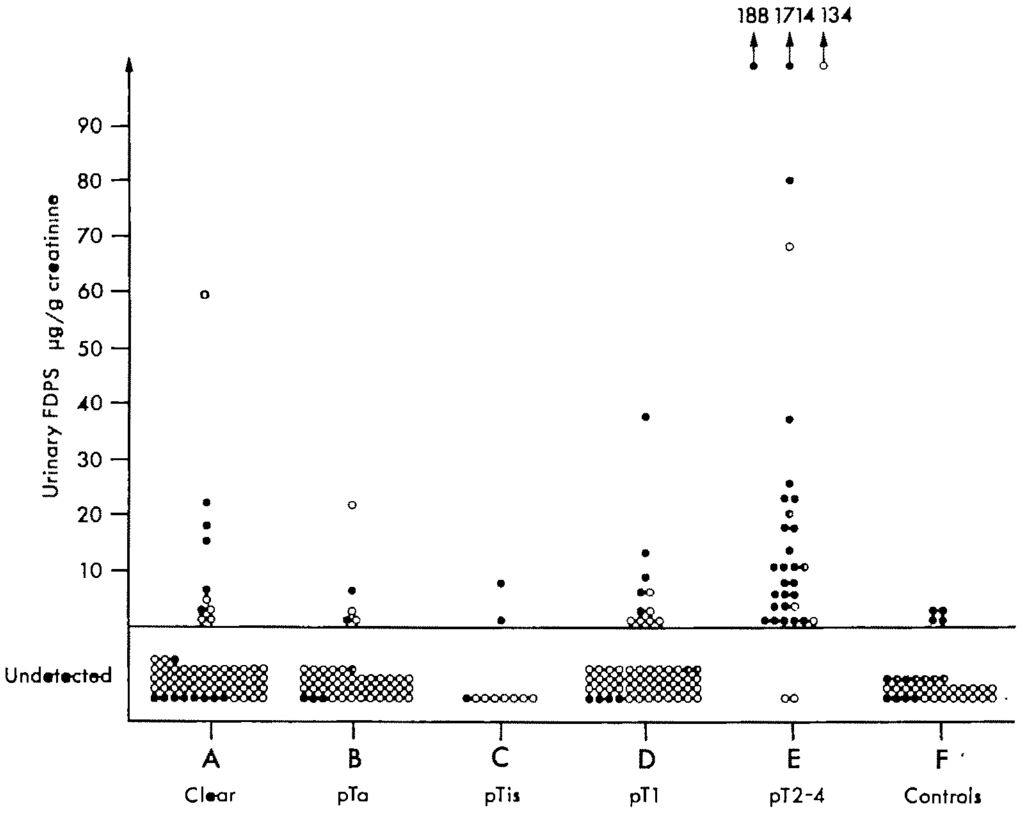

Fig. 1 Urinary FDPs in carcinoma of the bladder and controls. (● = albuminuria, ◐ = albumin unknown; ○ = no albuminuria).

shown in Table 2 and Figure 2. A level greater than 50 µg/g creatinine was regarded as raised. The deeply invasive tumour group (pT2–4) had the greatest percentage of urines with raised albumin (80%) and the greatest mean value compared with other groups ($P<0.001$; standard χ^2 test). There was no statistical difference between the other groups when compared with each other ($P>0.1$). Statistical analysis indicated that group E had significantly higher elevated albumin values than for the equivalent elevated values for the other groups combined ($P<0.01$; non-parametric Kruskal-Wallis test).

Analysis of specimens with both elevated FDPs and elevated albumin showed the difference between group E and the other groups to be highly statistically significant ($P<0.001$; standard χ^2 test).

Table 3 shows the results of urine cytology for each group. Group E once again had the highest percentage of abnormal cytologies. In groups A to D the percentage of abnormal cytologies was higher

Table 2 Albuminuria in Patients with Transitional Cell Carcinoma and Controls

Group	*Histology*	*Specimens Examined*	*Specimens with albuminuria 50 µg/g creatinine*	*% Elevated*	*Mean value albumin µg/g creatinine*
A	Clear	60	15	25.0	46.4
B	pTa	46	5	10.9	12.4
C	pTis	10	3	30.0	36.1
D	pT1	57	9	15.8	42.4
E	pT2–4	31	25	80.6	285.1
F	Controls	28	8	28.6	37.5

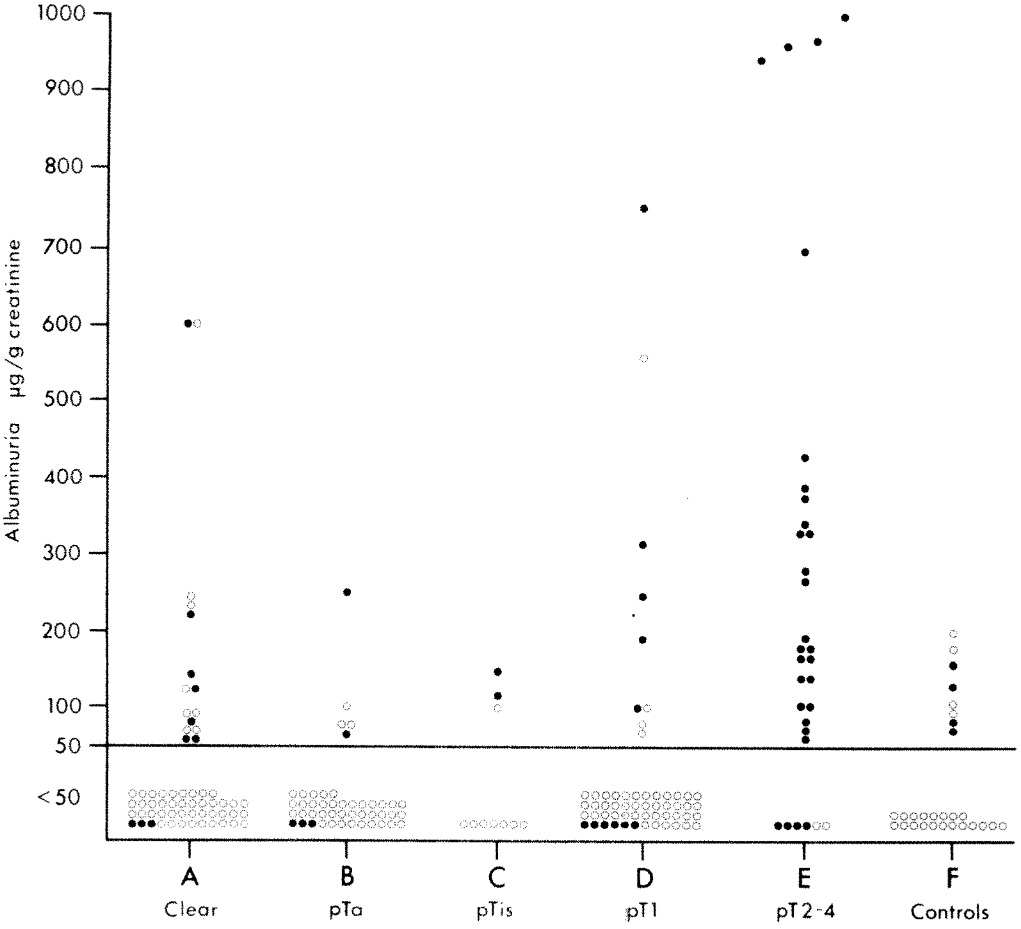

Fig. 2 Albuminuria in carcinoma of the bladder and controls. (● = urinary FDPs present; ○ = no urinary FDPs present).

than the percentages of elevated FDPs and albumin.

In groups A to D, 28 patients had detectable urinary FDPs. Seven of these had presented previously with deeply invasive bladder tumours (pT2–4). Renal stones were found in a further three patients and hydronephrosis had been diagnosed previously in three patients.

Microscopic haematuria was present in 31 patients at the time of cystoscopy. Table 4 shows the relationship of urinary FDPs to microscopic haematuria. It did not affect whether FDPs were present in the urine or not (not significant; binomial probability test). Similarly, in Table 5 the presence of a urinary tract infection in 19 patients at the time of cystoscopy did not affect the presence of urinary FDPs (not significant; binomial probability test).

Table 3 Abnormal Urine Cytology in Patients with Transitional Cell Carcinoma and Controls

Group	*Histology*	*Specimens examined*	*Specimens with positive cytology*	*Specimens with suspicious cytology*	*Abnormal cytology*
A	Clear	54	6	11	31.5
B	pTa	38	5	9	36.8
C	pTis	10	6	1	70.0
D	pT1	51	15	14	56.9
E	pT2–4	30	17	6	76.7
F	Controls	32	0	3	9.4

Table 4 Patients with Microscopic Haematuria (n = 31)

	Tumour present	*Tumour absent*
FDPs positive	13	3
FDPs negative	12	3

Table 5 Patients with Urinary Tract Infection (n = 19)

	Tumour present	*Tumour absent*
FDPs positive	6	0
FDPs negative	9	4

Discussion

O'Meara and Jackson (1958) showed that fibrin was deposited around the peripheral cells of actively growing tumours in the human. This fibrin deposition may provide an advantage to the neoplastic cells by interfering with the free circulation of tissue fluid which bathes the normal cells. The fibrin also forms a framework on which the malignant cells grow (O'Meara, 1958).

Fibrin and hence fibrinogen degradation products are formed in actively invading tumours. In this series, FDPs were found in the majority of urines of those patients with deeply invading bladder tumours (group E). These results reflect the work of O'Meara (1958).

There is controversy as to how the FDPs get into the urine. There may be a transudation of the degradation products directly into the urine in the bladder. Local transudation of albumin accompanying fibrin deposition and subsequent fibrinolysis could account for the correlation between albuminuria and urinary FDPs.

Alternatively, the FDPs may pass into the urine through the glomeruli. This may occur as a result of a glomerular lesion caused by the deposition of tumour derived antibody antigen complexes. Hemmingsen *et al.* (1981) suggested this method of excretion for a variety of proteins found in the urine of patients with bladder tumours. Renal tubular lesions may also exist. Yu *et al.* (1983) found that 26% of patients with superficial bladder tumours and 35% of patients with advanced lesions had increased excretion of alpha-1-microglobulin in their urine. They showed that alpha-1-microglobulin is an indicator protein for renal tubular function. Both glomerular and tubular abnormalities may be responsible for the FDP excretion. All of the other known causes of increased excretion of urinary FDPs (renal stones; glomerulonephritis; upper urinary tract infection and renal transplant rejection) are diseases of the upper urinary tract. In particular, lower urinary tract infection (which is a common cause of haematuria) is not associated with elevated FDPs (McCabe *et al.* 1984).

From this series, FDPs in the urine are markers of tumour invasion. This assumes that other conditions which are known to be associated with elevated FDPs (upper urinary tract infections, renal transplant rejection, renal stones and glomerulonephritis) are absent. Our results agree with those of Jayachandran *et al.* (1984). The FDPs were a more accurate marker in the deeply invasive group (pT2–4). Urinary FDPs are of no value in screening for the presence of a bladder tumour because only 17% of urines from patients with superficial bladder tumours had detectable levels of FDPs. Longer follow-up is required to determine whether the raised urinary FDPs in the patients with superficial lesions represent a true false positive result or are identifying those tumours which will become invasive.

The distribution of albuminuria in each group was similar to that of the urinary FDPs. In group E (pT2–4) the vast majority of urines that contained detectable FDPs also had elevated albumin. If the glomeruli were damaged by antigen-antibody complexes, resulting in an increased filtration of plasma proteins, then albuminuria would be expected since it is the classical sign of glomerular damage.

Cytology is a useful and common adjunct to cystoscopy in the management of bladder neoplasia. In this series it was more accurate than FDPs or albumin in predicting the overall presence or absence of tumour. Cytology was more accurate in the superficial tumour groups than FDPs or albumin, but less so in the deeply invasive tumours.

The presence of renal stones can produce false positive FDP levels but urine cytology can also be inaccurate in the same conditions.

Measurement of FDPs could be used to monitor superficial lesions to detect early invasion and to monitor patients after total cystectomy and ileal conduit formation (Jayachandran *et al.*, 1984). Unfortunately, if the FDPs are excreted through the glomeruli it is not known if the damage done to the glomeruli by the antigen-antibody complexes is reversible or not.

We believe that urinary FDPs have a role in the management of patients with bladder tumours as a marker of tumour invasion. Further longitudinal studies are required to assess their long-term use.

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Bilharziasis in Malignant Tumours of the Urinary Bladder

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Summary—In a review of 2248 cystoscopic examinations conducted over 10 years, malignant tumours of the urinary bladder were found in 172 patients. In 128 of these the condition was associated with bilharziasis. The lateral wall of the bladder was the commonest site (52.3%).

Squamous cell carcinoma occurred in 78.1%. Forty-nine patients refused surgery and eight were found to have advanced inoperable tumours. Seventy-one patients had a total cystectomy. There were no operative deaths but post-operative complications occurred in nine cases. Eight patients died within 2 years but 21 were well and tumour-free at 5 years.

It was concluded that there is a marked association between bilharziasis and bladder cancer. When the tumour is operable, cystectomy is the treatment of choice.

Urinary bilharzial disease is common among non-Kuwaiti people who come to work in Kuwait. The absence of rivers and lakes makes it impossible to be affected by bilharziasis inside Kuwait.

Ureteric strictures (Al-Shukri and Alwan, 1983) and bladder cancer (Ferguson, 1911; Shamma, 1955; El Sebai, 1981) are frequently associated with urinary bilharziasis.

According to the Kuwait Cancer Control Registry (1979-1982), the crude incidence of all bladder cancer was 1.6/100,000 in Kuwaiti males but 4.4/100,000 in foreign resident males. It was less than 0.1/100,000 in Kuwaiti females compared with 1.8/100,000 in foreign resident females. It was the third commonest cause of death after cancer of the bronchus and liver in both groups (8.2% of Kuwaiti males; 6.9% of foreign male residents). In females, breast cancer was the commonest tumour. Bladder malignancy ranked sixth in incidence in Kuwaiti females (3.9%) and eighth (4.1%) in foreign resident females.

We have reviewed our patients with bladder cancer and compared the results with the experience of others in countries where the disease is endemic.

Patients and Methods

During the 10 years from September 1974 to September 1984, we performed 2248 cystoscopic examinations. Bladder cancer was discovered in 172 patients (7.7%). Bilharziasis was present in 128 of these (7.4%). There were 126 males and two females, their ages ranging between 20 and 60 years (mean 45).

All patients were evaluated clinically and had routine laboratory and radiological investigations. Many had abdominal ultrasound examinations, CT scans, skeletal survey and bone scans. All were cystoscoped. The site and shape of the tumours were noted and TUR biopsies were taken in most cases. When good visualisation was difficult a punch biopsy was taken. The size, location and mobility of the tumours were estimated bimanually.

Eight of the 128 patients were found to have advanced disease unsuitable for surgery. In 49 cases the tumour was removable but the patients refused surgery. Seventy-one patients (55.5%) had a total cystectomy, removing as much urethra as possible by the abdominal route. Dissection included the pelvic lymph nodes, but more extensive lymph node dissection at the aortic bifurcation and para-aortic region was performed in only a few patients.

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Diversion was by an ileal conduit in 60 cases and ureterosigmoidostomy in the remainder.

Pre-operative and post-operative radiotherapy (2000 and 4000 rads respectively) was given to three patients with transitional cell carcinoma. One patient with sarcoma received a full course (4000 rads) of post-operative radiotherapy. Four patients had stage P4 tumours and it was hoped that post-operative radiotherapy to the para-aortic lymph node area and lateral walls of the pelvis might improve their prognosis.

Results

Table 1 shows the location of the tumours in the bladder. The lateral wall was the commonest site (52.3%), while both the vault and the bladder neck were the least affected (4.7% each). In 18 patients (14.1%) either multiple tumours were found or the tumour was so extensive as to fill the bladder.

Table 2 shows the histology of the biopsies and Table 3 shows the histology of the 71 cystectomy specimens. In all cases heavy bilharzial infestation was demonstrated. In the cystectomy specimens the tumours were well and moderately differentiated carcinomas in 88% of cases and poorly differentiated in the remainder. They were staged as P3 in 76% and P4 in 24%. The single sarcoma was a moderately differentiated P4 tumour. The lymph nodes showed no evidence of metastasis in any of the carcinoma patients but were positive in the patient with sarcoma.

There was no mortality but post-operative complications occurred in nine patients (12.7%). Seven developed wound infection, one had a temporary urine leak and another had delayed paralytic ileus.

Table 1 Site of the Tumours

Lateral wall	67 (52.3%)
Trigone	23 (18%)
Multiple or extensive	18 (14.1%)
Posterior wall	8 (6.2%)
Vault	6 (4.7%)
Bladder neck	6 (4.7%)
Total	128 (100%)

Table 2 Histology of 128 Cystoscopic Biopsies

Squamous cell carcinoma	100 (78.1%)
Transitional cell carcinoma	23 (18%)
Adenocarcinoma	4 (3.1%)
Anaplastic carcinoma (sarcoma in cystectomy specimen)	1 (0.8%)
Total	128 (100%)

Table 3 Histology of 71 Cystectomy Specimens

Squamous cell carcinoma	54 (76.1%)
Transitional cell carcinoma	12 (16.9%)
Adenocarcinoma	4 (5.6%)
Sarcoma	1 (1.4%)
Total	71 (100%)

Follow-up ranged from 1 to 5 years. During the first year all 71 patients were well and tumour-free, except for the sarcoma patient who developed abdominal metastases after 4 months. He returned home and was lost to follow-up. At 2 years, eight of the 59 patients we were able to follow up died from distant metastases to the liver or lungs with or without local recurrences, but 51 remained well and tumour-free. Of the eight who died, three were from the transitional cell carcinoma group who received radiotherapy; the other five had squamous cell carcinoma. All of these patients had poorly differentiated carcinoma, stage P4. At 5 years, 21 of the 37 patients followed up (56.8%) remained well and tumour-free and 16 were lost to follow-up. Only five were followed up for more than 5 years.

Generally, no difference in the survival rate at 2 and 5 years was found between patients with squamous cell, transitional cell or adenocarcinomas.

Discussion

In reviewing 425 bladder biopsies of patients treated in Basrah (Iraq), Al-Adnani and Saleh (1983) found bladder carcinoma in 254. Seventy of these (27.6%) were associated with bilharziasis. Reports from Egypt (El-Sebai *et al.*, 1973; El-Sebai, 1977) showed a considerable variation in incidence from 25 to 40%. The association between the two conditions was much higher in our patients (74.4%). This could be attributed to the larger number of patients in the present series, to the possible failure to note bilharzia in the biopsies examined, or to the marked selection bias stated in the Egyptian reports. El-Sebai (1973) indicated that bladder cancer patients were not usually admitted to most of the treatment centres and figures related to the National Cancer Institute (Cairo) were obtained solely from pathology records.

Our finding of only two female patients differed from that of El-Sebai (1978) and El-Boulkany *et al.* (1972), who noted a male:female ratio of 5:1 in Egypt. In Baghdad (Iraq) the male:female ratio was 2.5:1 (Talib, 1970) and Al-Adnani and Saleh (1983) reported an incidence of 4:1 in Basrah (Iraq). Prates (1962) noted an equal occurrence between the sexes in Mozambique. The probable reason for this difference is that the above studies were carried out in endemic areas where both sexes were found in equal numbers; in Kuwait, however, the number of men coming to work in the country greatly outnumbers the women. A mean of age of 45 years in our patients is similar to that found in other studies (El-Boulkany *et al.*, 1972; Al-Adnani and Saleh, 1983).

Although IVU and cystoscopy with biopsy remain the classical way of diagnosing bladder carcinoma, in recent years ultrasound studies (Fig. 1) and CT scans (Fig. 2) provide important additional information by showing the bladder tumour and its extent. Although in both examinations the tumour was clearly shown, the CT scan gave more information than ultrasound, particularly with regard to lymph node enlargement. Lymphography was not used routinely because it can give misleading results; also, lymph node metastasis is relatively rare in bilharzial bladder cancer.

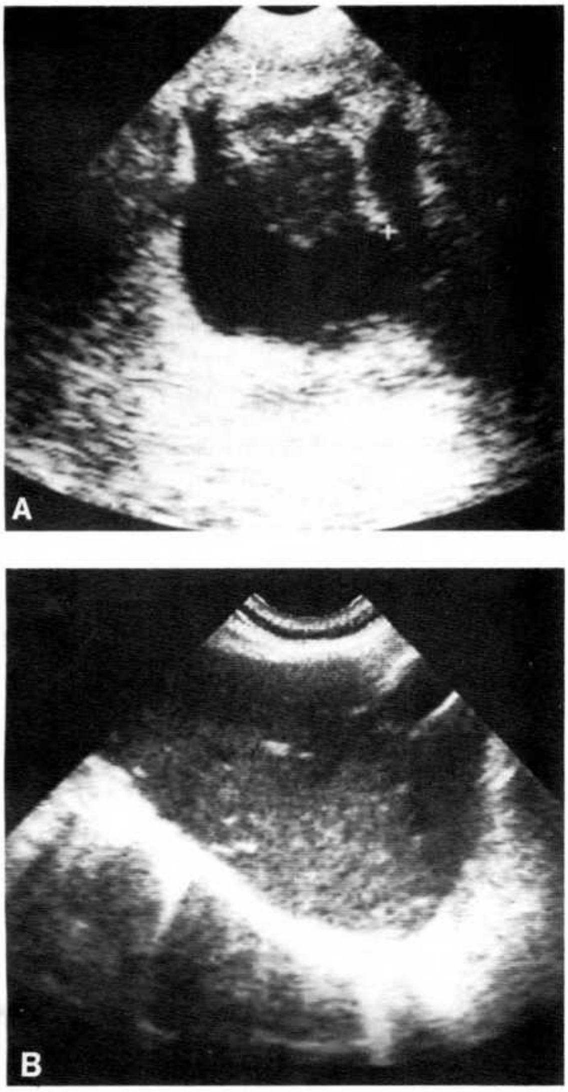

Fig. 1 (A) Ultrasound showing the tumour inside the bladder. (B) Ultrasound showing a larger tumour.

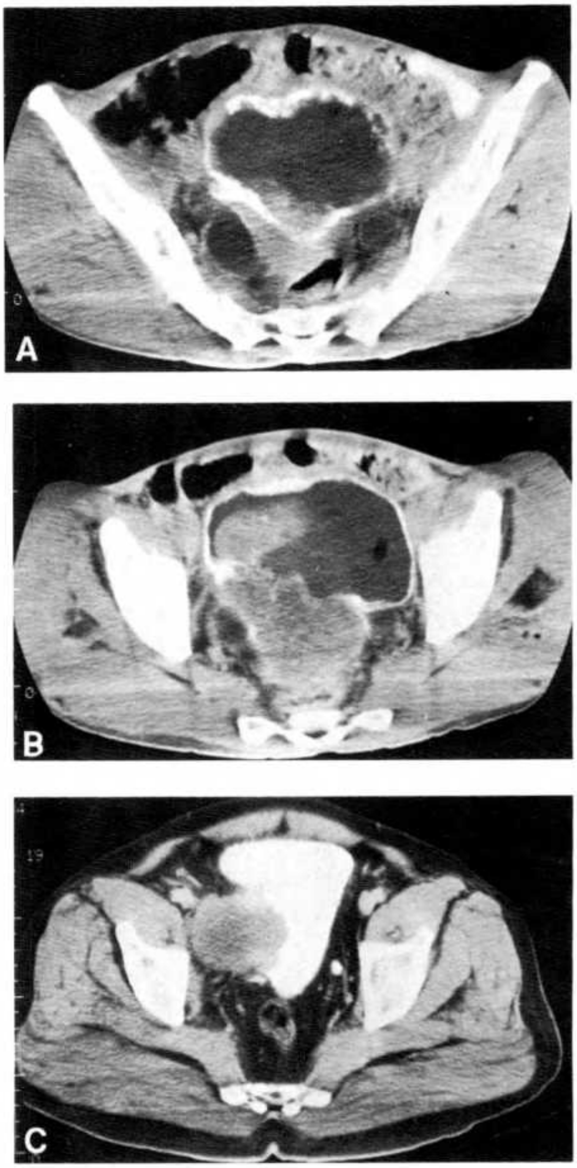

Fig. 2 (A) CT scan showing the tumour posteriorly in the bladder. The round shadows on each side of the rectum are the dilated ureters. (B) CT scan of same patient showing the extent of the tumour. The ureters are also shown. (C) CT scan of another patient showing the tumour in a bladder filled with dye.

The frequent occurrence of these tumours on the lateral walls and base of the bladder in this series coincides with the findings of other workers (El-Boulkany *et al.*, 1972). Chronic urinary bilharziasis is usually complicated by various metaplastic and proliferative changes in the bladder epithelium which are also frequently present in patients with established bladder carcinoma (Ishak *et al.*, 1967; Khafagy *et al.*, 1972). In the present study, tumours were of the fungating squamous cell type with remarkable keratinisation. Both this finding and the proportion of different histopathological types resemble the findings reported from Iraq and Egypt (El-Sabai, 1978; Al-Adnani and Saleh, 1983).

The relatively infrequent lymph node metastasis in bilharzial carcinomas compared with non-bilharzial carcinomas could be explained by the fibrosis and calcification of the bladder in this disease. Nevertheless, with high grade tumours, lymphatic and vessel invasion is to be expected (Mostofi *et al.*, 1973).

Since most of our patients were not permanent residents in Kuwait, regular follow-up was difficult. Of the 37 patients followed up, however, 21 (56.8%) were well and tumour-free at 5 years and 16 were lost to follow-up.

Ghoneim *et al.* (1976) found that after correlating the survival figures with the various tumour parameters, the squamous cell and transitional cell carcinomas have essentially the same prognosis. Our results confirm this finding. Ghoneim *et al.* (1976) also stated that the most critical prognostic indices are tumour grade, stage and lymph node involvement.

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Phenoxybenzamine in Prostatic Hypertrophy
A Double-blind Study

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Summary—Forty-five patients awaiting prostatectomy participated in a double-blind study of phenoxybenzamine 10 mg/day for 5 weeks. Objective measurements of peak urine flow, voided volume, residual urine and frequency of micturition and nocturia showed no significant difference between phenoxybenzamine and placebo. Patients taking phenoxybenzamine had a significantly greater improvement in hesitancy and flow symptoms than those on placebo. Side effects occurred in 47 6% of patients on phenoxybenzamine and 22.2% of those on placebo. In this study phenoxybenzamine 10 mg/day was ineffective in patients with benign prostatic hypertrophy.

Alpha-adrenergic receptors in the prostate are a factor in the symptomatology of patients with bladder outflow obstruction due to benign prostatic hypertrophy (Caine *et al.*, 1975). Clinical trials have shown benefit with the alpha-blocking drug phenoxybenzamine (Boreham *et al.*, 1977; Caine *et al*, 1978; Abrams *et al*, 1982). Others have, however, suggested that the drug was ineffective at lower doses (Brooks *et al.*, 1983, Griffiths and Schroeder, 1984).

The aim of this study was to assess the effect of phenoxybenzamine 10 mg/day against placebo on urine flow rates and urinary symptoms in patients awaiting prostatectomy who had bladder outflow obstruction due to benign prostatic hypertrophy.

Patients and Methods

Forty-five patients (mean age 63.3 years, range 44-80) entered the double-blind study. Three patients randomised to phenoxybenzamine and three to placebo were withdrawn because of non-attendance and a further two because of side effects. Thirty-seven patients therefore completed the study.

Patients with severe ischaemic heart disease, diabetes, cerebrovascular disease, those taking drugs with known effects on the bladder or beta blockers and those requiring urgent surgery were excluded. Patients were assessed symptomatically and objectively. On entry to the study, residual urine was measured by urethral catheterisation Peak urine flow rates were measured with a DISA 21 F01 Mictiograph. Micturition diaries were used to record frequency and nocturia and patients completed these for the 7 days prior to each hospital visit. After 14 days' initial assessment, peak urine flow rates were repeated and patients randomly allocated to 10 mg phenoxybenzamine/day or placebo. Following 4 weeks' treatment, peak urine flow rates and residual urine were measured together with symptomatic assessment. The final review was after 5 weeks' treatment, when peak urine flow rates were repeated.

The statistical methods used were paired *t* tests, non-parametric sign test, 2 sample *t* test, non-parametric Mann Whitney U test, chi-squared test and Fisher's exact test with Tocher's modification.

Results

Residual urine decreased for both phenoxybenzamine ($\alpha < 0.04$) and placebo groups ($\alpha < 0.006$). Nocturia significantly decreased both on drug and

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Table 1 Results of Objective Measurements in 37 Patients (mean figures)

	21 patients on phenoxybenzamine		*18 patients on placebo*	
	Pre-treatment	*Post-treatment*	*Pre-treatment*	*Post-treatment*
Peak urine flow rate (ml/s)	6.4	7.8	6.6	8.3
Residual urine (ml)	114.2	72.9	120.9	73.8
Voided volume (ml)	191.4	175.5	125.9	148.1

placebo ($\alpha < 0.001$). There was no difference between phenoxybenzamine and placebo as regards pre- and post-treatment changes in peak urine flow rate, voided volume, residual urine or the ratio of volume voided to total bladder volume (Table 1).

Subjective symptoms (hesitancy, urgency and slow stream) were all significantly improved ($\alpha < 0.05$) after phenoxybenzamine but not after placebo (Table 2). There was no difference between the two groups as regards frequency and nocturia.

All patients were in the obstructed category before starting treatment using flow-rate nomograms (Siroky *et al.*, 1979). One patient on phenoxybenzamine and one on placebo were unobstructed after completing the trial.

Side effects (Table 3) occurred in 10 patients on phenoxybenzamine (47.6%) and four on placebo (22.2%). Two patients, one on phenoxybenzamine and one on placebo, developed headaches and hypertension and were withdrawn from the trial.

Discussion

Following the demonstration of high alpha-adrenergic receptor activity in the human prostate (Caine *et al.*, 1975), alpha-adrenergic blockade was advocated in benign prostatic hypertrophy (Caine *et al.*, 1976). In an uncontrolled study, Boreham *et al.* (1977) used phenoxybenzamine 10 mg twice daily for 7 days in 30 men awaiting prostatectomy. Symptoms were improved in 18 and 10 showed urodynamic benefit. However, only one-third of the patients remained free of side effects. Caine *et al.* (1978) used phenoxybenzamine 10 mg twice daily for 14 days in 49 patients in a double-blind study. Frequency and nocturia were significantly reduced and peak and mean urine flow significantly increased. Residual urine was unaffected. Side effects were noted in 11 of 24 patients on phenoxybenzamine. Abrams *et al.* (1982) used phenoxybenzamine 10 mg twice daily for 4 weeks in 41 patients. The symptoms of hesitancy and slow stream were significantly improved and peak urine flow and residual urine were also significantly increased. The same authors also used phenoxybenzamine 5 or 10 mg/day in 34 patients and reported a significant increase in urine flow rate and a fall in residual urine with no patients leaving the study because of side effects.

Table 2 Results of Subjective Measurements in 37 Patients (mean figures)

	21 patients on phenoxybenzamine		*18 patients on placebo*	
	Pre-treatment	*Post-treatment*	*Pre-treatment*	*Post-treatment*
Frequency	8.1	7.6	8.7	8.9
Nocturia	2.0	1.5	3.3	2.6

Table 3 Side Effects

Side effect	*Phenoxybenzamine (21 patients)*	*Placebo (18 patients)*
Tiredness	3	0
Postural dizziness	2	0
Abdominal distension	2	0
Headache/hypertension	1*	1*
Nausea	1	1
Retrograde ejaculation	1	0
Nasal discharge	1	0
Periorbital discomfort	1	0
Difficulty focusing	1	0
Ankle swelling	0	1
Depression	0	1

Note: more than one side effect in two patients.
* Withdrawn from study.

Brooks *et al.* (1983) used phenoxybenzamine 10 mg/day in 27 patients and showed no statistically significant benefit on flow rate or residual urine. They concluded that phenoxybenzamine in low doses was ineffective in the treatment of benign prostatic hypertrophy. Griffiths and Schroeder (1984) studied 16 patients using both 10 and 20 mg phenoxybenzamine. Of those on the active drug, 70% reported side effects such as impotence, dizziness or nasal stuffiness. There was no significant difference between the groups as regards symptomatic improvement and peak urine flow rates and residual urines were not improved. Nocturia was significantly improved on 10 mg phenoxybenzamine but this was not the case in the present study.

Phenoxybenzamine 10 mg/day was used in this series and side effects occurred in 47.6% of patients on the active drug. Because of concern about postural hypotension, patients were instructed to take their medication on retiring and this was the only side effect they were specifically warned about. However, it was not a major problem in our patients, although the difficulty of conducting a truly double-blind trial because of worries about postural hypotension has been pointed out by Abrams *et al.* (1982). Of the two patients who developed headaches and hypertension, one was taking phenoxybenzamine and the other was on placebo. For hypertension to develop while taking an alpha-blocker is paradoxical and may have been coincidence. No significant differences were demonstrated between the two groups as regards peak urine flow, residual urine, frequency and nocturia. From the subjective point of view, hesitancy and slow stream improved on active treatment only. It is of interest that residual urine decreased in both groups and this was possibly an effect of bladder training.

It was concluded that phenoxybenzamine 10 mg/day was ineffective in patients with benign prostatic hypertrophy.

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Urethral Rhinosporidiosis
Analysis of 27 Cases

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Summary—An analysis of 27 cases of urethral rhinosporidiosis is presented. Only 11 cases have been previously reported. The disease is chronic and causes no systemic derangement. The key to diagnosis is its characteristic histology and diathermy excision provides the best treatment.

Rhinosporidiosis is a chronic granulomatous condition usually affecting the anterior nares and commonly found in India and Sri-Lanka. The bulk of the literature on the subject has come from these two countries (Karunaratne, 1964; Kameswaran, 1966). The lesions form sessile or pedunculated polypoid masses which are highly vascular and friable. The nasopharynx, conjunctiva, lacrimal sac, skin, larynx, vagina, vulva and rectum are uncommon sites of the lesions (Mohapatra, 1971).

The literature offers very few cases of urethral rhinosporidiosis and suggests that it is rare. Dhayagude reported the first case of urethral rhinosporidiosis in 1941 and between then and 1983 only 11 cases have been reported (Palaniswami and Bhandari, 1983).

Our 27 cases constitute the first series of urethral rhinosporidiosis and we report for the first time its occurrence in the female urethra.

Patients

The hospital records of the Division of Urology from 1968, when the department was established, to 1984 were reviewed and 27 cases of histologically documented urethral rhinosporidiosis were found.

All of the patients came from a predominantly rural and agricultural area within a radius of 40 to 50 miles of Calicut, a coastal city in North Kerala, replete with paddy fields, ponds, rivulets and lakes.

The series included only two females, both in their mid-forties. The males ranged between 15 and 37 years of age. But for their urethral lesions, all patients were physically sturdy and healthy and without associated diseases such as diabetes mellitus, tuberculosis and hypertension. Appropriate serological studies gave no suggestion of sexually transmitted disease. All spouses of the married patients were free from rhinosporidiosis. None of the patients practised sexual aberrations such as sodomy.

All had almost identical clinical features consisting of urethral bleeding, a visible mass in and around the external urethral meatus and periodic voiding difficulties when the lesions mechanically impeded the flow of urine.

Urethral rhinosporidiosis usually restricts itself to the fossa navicularis and external urethral meatus but in two cases the spongy urethra as far as the penoscrotal junction was filled with numerous pedunculated and sessile lesions.

In the series as a whole, the lesions were mostly discrete, vascular, friable, painless, polypoid and pedunculated and some were sessile. In a few cases pedunculated and sessile lesions coexisted (Fig. 1). The differential diagnoses include non-specific granulomas and condylomata acuminata and lata.

The most common urethral lesion (51.9%) was solitary, pinkish, tongue-shaped and pedunculated, arising from the floor or walls of the fossa navicularis (Fig. 2). When fully drawn out, it measured 2 to 3 cm and bled readily. In a few instances these long-stalked lesions remained in the fossa navicu-

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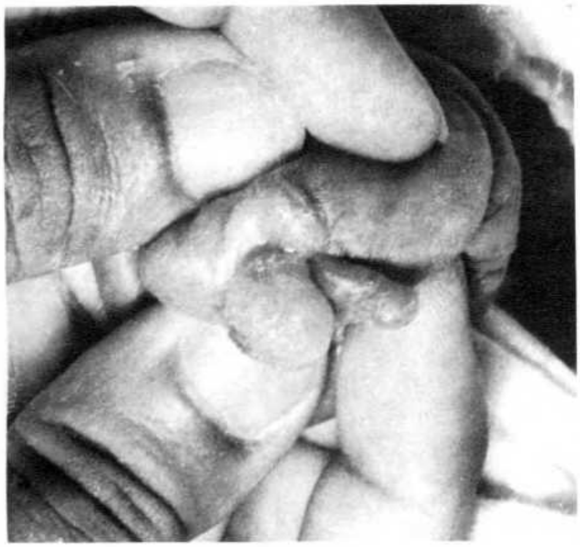

Fig. 1 Pedicled and sessile lesions.

laris except during voiding. There were instances when large portions of friable and pedicled lesions broke off with such trauma as changing undergarments. This did not lead to a cure, however, since the residual stalk grew steadily to its original size. One patient periodically amputated digitally the protruding portion of his urethral lesion, but the benefit was only transitory.

Excessive adherent surface mucus and mature sporangia projecting beneath the surface epithelium as small white or translucent dots often characterise the lesions (Karunaratne, 1964; Mohapatra, 1971). These features are rarely seen in the urethra but they were noted in one of the female urethral lesions (Fig. 3).

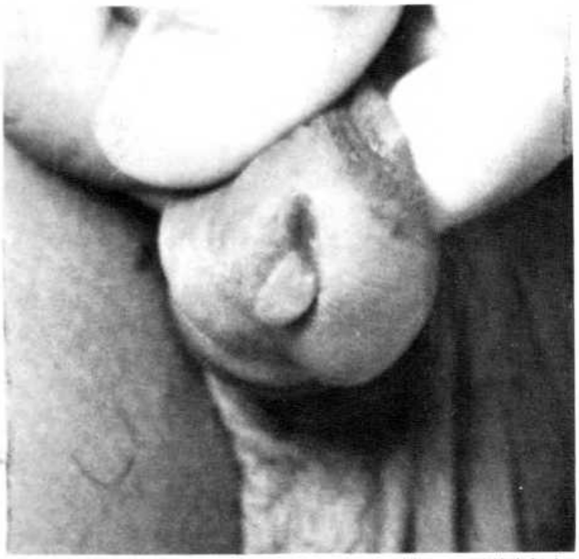

Fig. 2 Most common form of urethral rhinosporidial lesion emerging from fossa navicularis.

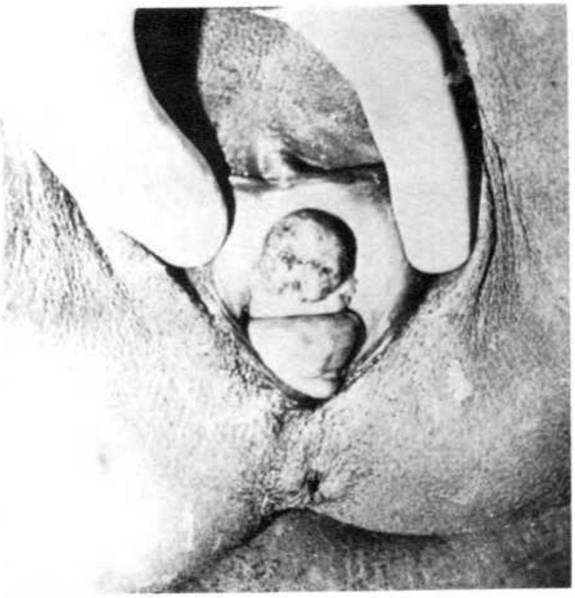

Fig. 3 Globular lesion covered with mucus and studded with white dots representing mature sporangia.

A male urethral rhinosporidial lesion closely simulated a soft tissue tumour and appeared as a soft oval mass 2.5 cm in length which hung from the left lateral wall of a marginally hypospadiac urethral meatus. The outer epithelial envelope of the mass was indistinguishable from that of the glans penis in both texture and colour (Fig. 4). The ventral surface of the swelling harboured a small elliptical window displaying red granulation-like tissue.

The urethral lesions reviewed in this series developed over a period of 3 to 15 months and showed no tendency to heal spontaneously. There were seven cases of single recurrences in this series (25.9%), three of which we believed were the result of re-infection. All recurrences were successfully treated, great care being exercised during excision.

Discussion

The causative agent, *Rhinosporidium seeberi*, is usually accepted as being a fungus, although the exact taxonomic position of the parasite has not yet been clearly established (Ashworth, 1923).

The fungus commences its life cycle as a parasite measuring 8 μ. It grows by nuclear division until it

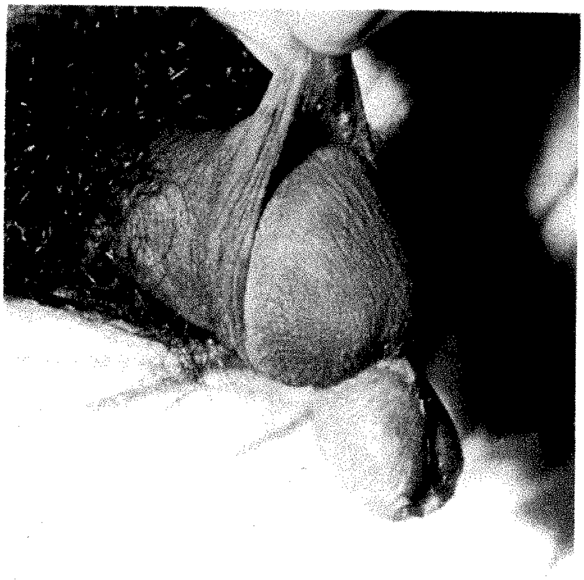

Fig. 4 Lesion simulating a soft tissue tumour.

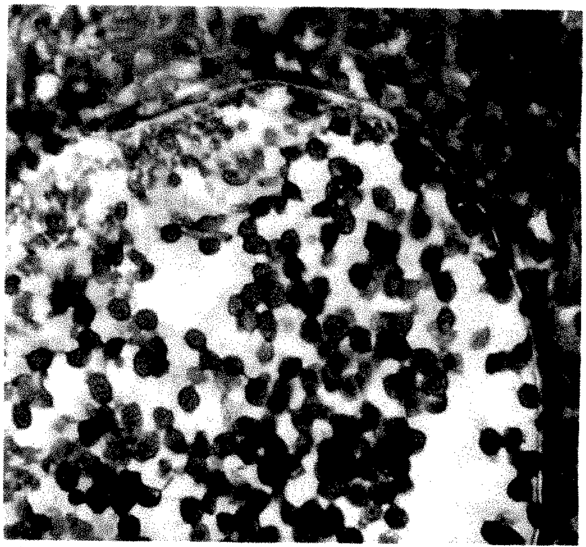

Fig. 5 Typical mature sporangium with double contoured chitinous envelope extruding spores. (H and E × 300).

reaches a size of 200 to 300 μ, when it contains over 4000 nuclei which form 16,000 spores (Boyd, 1970). A sporangium, which represents the mature parasite, has a double contoured chitinous envelope with a germinal pore through which the spores are extruded.

The pathogenic factors underlying the mode of infection or transmission have not yet been established and the parasite's free-living, saprophytic stage is unknown. Repeated attempts to cultivate the organism artificially or to transfer it to laboratory animals have been unsuccessful (Dube and Veliath, 1964). Similarly, attempts to convert the tissue phase of *Rhinosporidium seeberi* into the mycelial phase *in vitro* and *in vivo* have also been abortive (Ramachandra Rao and Jain, 1971). Contaminated water and soil are considered likely sources of infection and the rural background of our patients seems to substantiate this.

The disease usually afflicts the younger age group (20–40 years) and is more frequent in males than females.

A chronic and benign condition, with no systemic or constitutional effects, it is not contagious and seems not to be transmitted from man to man or from animals to man. The lesion is often localised to a single organ, but two fatal cases have been reported with disseminated lesions (Rajam *et al.*, 1955; Agarwal *et al.*, 1959).

Histological examination reveals a non-specific chronic cellular infiltrate encircling sporangia in different stages of maturity. The inflammatory component consists of lymphocytes, plasma cells and polymorphonuclear leucocytes. The more mature ones are subepithelial. The squamous epithelium covering the plypoid growths is hyperplastic and tends to invaginate. Mature sporangia enclosed by a double contoured chitinous envelope extruding spores are easily discernible (Fig. 5) and the fields are heavily strewn with such spilled spores.

Medical treatment, systemic or local, exerts little influence on the course of the disease, although agents such as trivalent and pentavalent antimony preparations have been tried (Mohapatra, 1971; Sharan, 1979). Surgical extirpation followed by electrocoagulation of the base is the only certain method of cure. Local infiltration of amphotericin B has been advocated as an adjunct to surgery to prevent re-infection and spread (Rippon, 1974). Complete excision is often helped by a generous meatotomy which clearly displays the base of the lesion.

Multiple lesions studding the entire pendulous urethra pose an awkward problem because transurethral fulguration or resection is fraught with the risk of urethral complications and dissemination of the disease. It is better to lay the urethra open, excise all lesions and reconstruct the urethra 6 months later. The lesion will recur if excision is incomplete.

Urethroscopy and urethrography are best avoided in the presence of untreated primary lesions.

In endemic areas, any odd-looking lesion at the external urethral meatus merits biopsy because urethral rhinosporidiosis is less rare than had previously been thought.

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Neonatal Testicular Torsion and Infarction: Aetiology and Management

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Summary—Thirty neonates presented with signs of testicular ischaemia over a 20-year period. Eighteen children had primary exploration revealing extravaginal torsion (10), intravaginal torsion (3), infarction without torsion (2) and torsion of the appendix testis (1). The other two children had simple biopsy of necrotic testes. In two instances the testis was untwisted and retained but both subsequently atrophied. The remainder underwent orchiectomy. Twelve children did not have initial exploration and 11 of these had subsequent testicular atrophy. At contralateral testis fixation, performed in 17 cases, signs of contralateral involvement in the ischaemic process were found in seven, suggesting that the primary event in the condition is infarction, with torsion occurring secondarily.

Since first reported in 1887, torsion of the neonatal testis has become well recognised and probably accounts for about 12% of all cases of testicular torsion (Brereton and Manley, 1980). Also well recognised and reported is testicular infarction in the neonate without demonstrable torsion (Johnston, 1968) but with physical and pathological features indentical to those found with torsion. Rather than postulate two separate processes, it has been suggested that idiopathic infarction represents torsion that has untwisted prior to exploration (Rhyne *et al.*, 1955).

Recent experience with an infant who was found to have testicular torsion on the right side associated with infarction of the appendix testis on the left side led to this review of 20 years' experience with these conditions and a review of the literature in a search for a common pathway for these findings.

Patients and Methods

The records of all infants under 1 month of age presenting in the period 1961 to 1980, with the clinical diagnosis of testicular torsion or infarction, were reviewed retrospectively.

Results

There were 30 patients in the series (Table 1). In 18 cases, primary exploration of the testis was performed. In 10, a typical extravaginal torsion of the spermatic cord was found. In eight instances the testis was deemed non-viable and was excised. On two occasions the testis was untwisted and left in place in the hope that some hormonal function might be retained. At follow-up, gradual atrophy

Table 1 Details of Patients

No. of patients	30	18	Left
		11	Right
		1	Bilateral
Age at presentation	Birth	16	
	2 days	4	
	3 days	3	
	4 days	4	
	1 week	1	Torsion of appendix testis
	3 weeks	1	Torsion of appendix testis
	4 weeks	1	Intravaginal torsion of undescended testis
Weight	25 patients		
	Range 2.72 to 4.2 kg		
	Mean 3.6 kg		
Delivery	24 patients		
	Vaginal	23	3 forceps
	Caesarean	1	

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occurred in both cases with only a small hard nodule remaining after 1 year.

Contralateral exploration was undertaken at the primary operation in four of these 10 infants with extravaginal torsion. One was the case reported above where an infarcted appendix testis was found, one had a normal testis but a wide mesorchium and the other two had normal findings apart from a simple hydrocele in one case. One child had contralateral exploration at 1 month of age because of a tense hydrocele and he was found to have a dusky testis with a free blood clot in the hydrocele. At follow-up 2 years later this testis was found to be larger than normal (4 ml size), having presumably undergone compensatory hypertrophy.

In addition, contralateral hydroceles were noted in four patients but were not explored.

In three of the 18 infants who had primary exploration, the torsion was found to be intravaginal around a wide mesorchium. Although one of these children presented late at 4 weeks of age with sudden onset of signs in an undescended testis, the other two presented in a manner identical to that of the extravaginal torsions. These two patients underwent exploration and fixation of the contralateral testis at the primary operation. The late presenter had an undescended testis on the contralateral side whilst the others had a normal contralateral testis.

Two of the infants who had primary operation were found to have infarction of the testis without demonstrable torsion. Both of these testes were excised and the contralateral side was not explored. A further child was found to have torsion of an appendix testis, the testis itself being unaffected. In two other infants, exploration was insufficient to determine the presence or absence of torsion. One of these children had bilateral testicular ischaemia and simple biopsy only was performed. Subsequently, both testes atrophied and the child received hormonal replacement and testicular prostheses at puberty. The other child also had only testicular biopsy and subsequent atrophy.

In 12 cases, primary exploration was not performed. Eleven of these children had the characteristic scrotal signs of neonatal testicular torsion and one had a hard bluish nodule beside an undescended testis and was diagnosed as torsion of an appendix testis. This child was lost to follow-up but the other 11 children subsequently had some atrophy of the affected testis. When reviewed 1 to 5 years later, seven had total absence of the testis, two with a larger than normal testis noted on the other side, whilst the remaining four were described as having pea-sized nodules palpable. Contralateral exploration and fixation were performed in 10 patients between 2 and 5 weeks after initial presentation. At this exploration, the contralateral scrotal contents were entirely normal in four cases. Two children were found to have a simple hydrocele with a patent processus vaginalis. Four children had hydroceles but no processus vaginalis could be demonstrated. This lack of processus was confirmed at inguinal exploration in two cases. One of these four children had marked testicular oedema and another marked oedema of the epididymis.

The contralateral findings are summarised in Table 2, combining findings at primary and delayed surgery.

Table 2 Findings following Contralateral Exploration in 17 Patients

Bilateral torsion	1
Torsion appendix testis	1
Hydrocele and oedema of testis	1
Hydrocele and oedema of epididymis	1
Hydrocele and free clot and dusky testis	1
Hydrocele and wide mesorchium	1
Hydrocele without processus	2
Simple hydrocele	2

Discussion

Torsion of the neonatal testis is a well recognised condition and has been the subject of a number of reviews (Lester and Gummess, 1961; Peterson, 1961; Guiney and McGlinchey, 1981). Most authors feel that torsion is usually a prenatal event and there is pathological evidence to support this (Myers, 1961; Peterson, 1961). The typical findings of scrotal discoloration and enlargement with no apparent tenderness are noticed soon after birth in an otherwise healthy infant. This condition seems to be confined to full term infants who are of above average birth weight. The average weight of 62 patients from this series and the literature was 3.66 kg, which is around the 60th percentile.

Either testis may be involved in torsion and although this series shows a preponderance of torsions of the left testis, of 108 cases from the literature and this series, 56 involved the left and 52 the right side. Bilateral torsion has been reported 13 times.

Surgery to excise the infarcted testis and fix the contralateral one seems to be the treatment of choice. The affected testis is almost invariably necrotic at operation. In 25 cases in the literature in which the testis was retained, only two did not undergo atrophy (Longino and Martin, 1955; Guiney and McGlinchey, 1981), although other successes are alluded to (Belman and Kaplan, 1981).

Contralateral exploration and fixation are certainly justified. In cases of intravaginal torsion there may be a contralateral anatomical abnormality likely to predispose to torsion, such as is frequently found in torsion in later life. A wide mesorchium that could predispose to torsion has also been found on the side opposite to an extravaginal torsion, both in one of the patients reported here and by Lyon (1963). The characteristic mobility of the neonatal testis extravaginally (Bellman and Kaplan, 1981) may also predispose to torsion in the neonatal period and there is some evidence that in cases of bilateral torsion, one testis may twist before the other (Gertsmann and Marble, 1980; Guiney and McGlinchey, 1981). Thus contralateral fixation, even when no intravaginal abnormality exists, may protect against contralateral torsion.

Primary testicular infarction without evidence of torsion has been recognised as occurring in the neonatal period for many years and is well documented (Fernicola, 1954; Johnson, 1968; Brereton and Manley, 1980). Although it has been suggested that this phenomenon is due to the untwisting before exploration of a previously twisted testis (Franzblau, 1956), there seems to be good evidence that spontaneous testicular infarction can occur. Emery and Mitchell (1957) reported a 20% incidence of minor testicular haemorrhagic infarction in 439 infant necropsies and in 19 cases there was complete haemorrhagic infarction of the whole testis. Although previous similar necropsy reports had related this finding to trauma from breech delivery (Spencer, 1892), Emery and Mitchell (1957) were unable to confirm this and concluded that haemorrhage occurred as a result of the rapid involution of the testicular interstitial cell mass that occurs around parturition.

Contralateral abnormalities such as reported here have not been highlighted in previous studies. However, a review of the literature reveals that the presence of a contralateral hydrocele has been noted before on several occasions—eight instances being reported in seven series (Ravitch, 1947; Longino and Martin, 1955; Rhyne *et al.*, 1955; Peterson, 1961; Lyon, 1963; Frederick *et al.*, 1967; Gelband and Wulfsohn, 1967). The presence of a communicating hydrocele on the contralateral side is probably of no significance and may well reflect the general incidence of this condition in the neonatal population. The presence of a reactive hydrocele around a twisted testis is common in older children and has been reported in neonatal torsion without a demonstrable processus vaginalis (Hyams, 1969). It is thus feasible that the contralateral hydroceles in this series were secondary to contralateral testicular pathology. However, it is possible that a contralateral hydrocele may result from the inflammation produced by the infarction of its neighbour.

In this series, not only were reactive hydroceles noted on the contralateral side, but four of the 17 patients who were explored exhibited other signs that ischaemia may have been affecting the contralateral testis, namely torsion of the appendix testis, a dusky testis with a clot in the hydrocele which may well have been the remains of an infarcted appendix, oedema of the testis weeks after contralateral infarction and oedema of the epididymis weeks after contralateral infarction. Oedema of the epididymis has been reported as a cause of "acute scrotum" in older children and is said to occur with small, spontaneous haemorrhage into the mediastinum testis (Brereton and Manley, 1980).

These observations may have a bearing on the understanding of the aetiology of testicular torsion in the neonate. Early theories suggested that the cause may be the trauma of a breech delivery causing haemorrhage and agonal torsion. Although this trauma does occur (Dunn, 1975), breech deliveries feature only rarely in reports of neonatal torsion.

The most popular current theory is that the extreme mobility of the neonatal tunica vaginalis within the scrotum allows torsion to occur due to some violent cremasteric contraction occurring *in utero* or during delivery. However, very strong cremasteric contractions can be observed in children of all ages sufficient to retract the testis from the scrotum but without causing infarction. Infarction without torsion does occur and, in this series, evidence can be found for bilateral involvement in the ischaemic process. It therefore seems more likely that the primary process is haemorrhagic infarction of the involuting testicular interstitium which, in the presence of favourable anatomy, results in infarction with or without torsion, torsion occurring agonally.

Neonatal testicular torsion and infarction, whilst not a common occurrence, is well recognised and can cause a management problem in the neonatal period. Primary exploration to untwist the involved testis rarely appears to salvage the testis from what is probably an antenatal event and may be primarily a vascular one. Contralateral exploration and fixation should be undertaken because abnormal testicular mobility at the mesorchium or supravaginal level may predispose to contralateral torsion. The primary pathological process underlying this condition may be spontaneous infarction.

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Testicular Tumour Markers in Spermatic Vein Blood

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Summary—The markers for testicular cancer, alpha-fetoprotein and human chorionic gonadotrophin, were measured in spermatic vein and peripheral blood taken at the time of orchiectomy. In all cases where markers were produced by the tumour, concentrations were found to be higher in spermatic vein than in peripheral blood, presumably because the former drains from the site of the tumour and dilution in the circulation has not yet occurred. Such measurements could be of particular value in patients whose tumours produce such small amounts of marker(s) that they are below the level of detection in peripheral blood.

The measurement of the markers alpha-fetoprotein (AFP) and human chorionic gonadotrophin (HCG) in the serum of patients with testicular cancer is now of established value in their management (Kohn and Raghavan, 1981).

Of all the blood samples taken for the monitoring of markers during the patient's treatment, one of the most important is that taken at or immediately prior to orchiectomy. If this is omitted and subsequent marker values are found to be normal, it is impossible to know whether the primary tumour was marker-secreting and hence whether any subsequent development of metastases might be accompanied by marker production. Even if post-orchiectomy marker concentrations are still elevated, the absence of a pre-operative estimation may diminish the accuracy and usefulness of marker half-life calculations.

Timbal and Rodier (1985) measured HCG in spermatic vein blood taken from testicular tumour patients at the time of orchiectomy. Their results indicated that, in some cases, HCG could be detected in spermatic vein blood but not in the peripheral blood.

The South West Testicular Tumour Study Group (SWTTSG) has recently commenced an investigation into concentrations of both AFP and HCG in spermatic vein blood taken at the time of orchiectomy (in addition to the usual peripheral blood sample), and preliminary results from this study are described here.

Patients and Methods

All eight patients studied were undergoing orchiectomy for removal of a suspected testicular tumour, and spermatic vein blood was obtained during this procedure.

Collection of spermatic vein blood is most simply achieved when the testis and its attached segment of cord have been removed. The clamp on the proximal end of the cord attached to the removed testis may then be taken off and the blood contained in the cord "milked" into a collection vessel.

Serum concentrations of AFP and HCG were measured using radioimmunoassays (IM.985 and IM.3094 respectively, from Amersham International).

Results

The results are shown in the Table. It can be seen that in all peripheral blood samples in which a marker was detectable, the concentration of that marker in spermatic vein blood was found to be higher, in some instances very much higher.

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Table Measurements of AFP and HCG in Serum from Peripheral Blood (PB) and Spermatic Vein Blood (SV) Taken at the Time of Orchiectomy from Testicular Tumour Patients

Patient	*Serum source*	*AFP (ku/l)*	*HCG (iu/l)*
DH	PB	105	151
	SV	204	389
TE	PB	<2	36
	SV	<2	510
GV	PB	96	<2
	SV	118	11
GF	PB	213	<2
	SV	299	4
JR	PB	6500	2000
	SV	7400	4500
AD	PB	25	3
	SV	35	12
MW	PB	<2	3
	SV	3	11
PT	PB	<2	13
	SV	<2	33

Discussion

It is assumed that marker concentrations in spermatic vein blood are higher than in peripheral blood because the spermatic vein drains directly from the site of the tumour and its contents have not yet undergone dilution in the peripheral circulation.

The results indicate that the value of marker measurements in the management of testicular tumour patients can be further enhanced if both spermatic vein blood *and* peripheral vein blood are taken at orchiectomy. However, it must be emphasised that the acquisition of the former does not remove the necessity for the latter, since all subsequent calculations of marker half-life during treatment and/or follow-up must be based on peripheral blood concentrations and, therefore, require that pre-operative value as the starting point.

Measurement of markers in spermatic vein blood could be of particular value in patients whose tumours produce only small amounts of AFP and/or HCG, such that they can be detected in spermatic vein but not in peripheral blood.

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Surgical Salvage of Advanced Testicular Tumours

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Summary—After combination chemotherapy, 19 patients underwent salvage surgery for testicular neoplasia. Active malignancy was found in nine patients, three of whom have died of the disease. Those with benign residual disease have had a good prognosis without further treatment. Biopsy alone of the residual masses proved reliable in determining which patients were to be simply followed or given further chemotherapy. If active malignancy was not resected fully, the prognosis was very poor. Our policy continues to be to attempt complete excision of residual masses after induction chemotherapy and to give salvage chemotherapy to patients with residual active malignancy.

The role of radical surgical removal of residual lymph nodes which may contain teratomatous metastases remains controversial.

The prognosis for testicular teratoma has improved dramatically with the introduction of combined cytotoxic chemotherapy (Samuels *et al.*, 1976). Higher complete remission rates using cisplatin in combination were reported by Einhorn and Donohue (1977). The results of the Medical Research Council Working Party on Testicular Tumours (1985) also confirms improved survival rates in 1981 and 1982 compared with earlier years. In 1981 and 1982, 100% of the patients in the MRC study received cisplatin and 78% received etoposide, whereas only 40% received cisplatin and 20% etoposide in previous years.

Primary surgical debulking followed by chemotherapy offers no advantage over chemotherapy alone (Javadpour *et al.*, 1982). It has been suggested that improved results are obtained by performing surgery after induction chemotherapy (Einhorn *et al.*, 1981). These workers claim that while combination chemotherapy will produce a 70% complete remission rate, a further 10% of patients can be rendered disease-free following surgical resection. More recently a surveillance policy has been adopted for residual masses (Levitt *et al.*, 1985). In this small series, salvage surgery was performed only when the residual mass enlarged. If the mass remained static and the patient's tumour markers were negative, then careful follow-up did not jeopardise the patient's final outcome.

If the histology of the residual mass shows no evidence of neoplasia or only mature teratoma, the prognosis is excellent (Brunner *et al.*, 1983; Tait *et al.*, 1984). Further chemotherapy for these patients may be unnecessary, but to exclude viable malignancy a complete excision is recommended (Donohue *et al.*, 1982). The tumour masses vary in composition and single biopsies may not be representative. There are no reliable pre-operative or intra-operative predictive criteria to indicate the precise histological nature of the residual disease (Donohue *et al.*, 1982).

Tait *et al.* (1984) reported that residual malignancy in the resected nodes, an incomplete resection and raised tumour markers at the time of post-chemotherapy surgery were all adverse prognostic features.

The bulk of the disease may be important. Longer survival was achieved in Stage IV disease compared with bulky Stage IIc in a series reported by Ringert *et al.* (1985). Since 20 to 30% of patients with residual masses and negative tumour markers will still harbour malignancy, histology remains the only certain way of knowing this (Vugrin *et al.*, 1981; Levitt *et al.*, 1985). Chemotherapy is indicated if active malignancy is found in the residual mass (Vugrin *et al.*, 1981).

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Patients

Since 1978, 19 patients have undergone salvage surgery for residual tumour following intensive combination chemotherapy in Leeds. Their ages at salvage surgery ranged from 17 to 50 years (mean 29.3). All cytotoxic regimes included cisplatin. Seventeen laparotomies were performed in 16 patients and four thoracotomies in three patients.

Of the 19 patients, 16 had initially presented with disseminated disease and three had progressed from Stage I disease. The Royal Marsden Hospital Classification of staging has been used (Hendry *et al.*, 1980).

Raised tumour markers (alpha fetoprotein and beta sub-unit human chorionic gonadotrophin) were found in 14 patients at presentation. The three patients who presented with stage I disease all had normal markers at initial diagnosis. The raised markers of all patients returned to normal after induction chemotherapy. Two patients (CG and SH) had elevated markers at the time of salvage surgery. The markers of both of these patients were normal at initial diagnosis.

Results

Details of the 19 patients are summarised in the Table. The tumour mass was completely removed in 11 patients and in one (DS) 80% was removed. Biopsies only were taken from the remainder as the surgeon considered the tumour mass to be inoperable.

In 10 patients mature teratoma or no evidence of neoplasia (usually composed of fibrosis and/or necrosis) was found. All are alive in either complete remission or a stable state. None of these patients has had subsequent treatment.

In one patient a single microscopic focus of "MTI" was found in his residual mass which was otherwise classified as mature teratoma. He has since had two courses of "top-up" chemotherapy.

The remaining eight patients were found to have residual active malignancy. All except one have received further chemotherapy and/or radiotherapy. Three have died of their disease. One patient (PAM) developed lung and bone metastases after an otherwise "curative" resection. He is now clinically free of disease following salvage chemotherapy and radiotherapy to the bone lesion.

One patient (CM) presented with an abdominal mass which was biopsied. The histology showed an anaplastic tumour. A subsequent testicular swelling proved to be a seminoma. He was treated with combination chemotherapy and radiotherapy but his abdominal mass persisted. At a second laparotomy the mass was totally resected and the histology showed a tumour compatible with a pancreatic islet cell tumour.

There was no operative mortality and the only

Table Results of Salvage Surgery of Advanced Testicular Tumours

Patients	*Histology of testis*	*Stage at salvage surgery*	*Histology of metastases*	*% Resected*	*Months from salvage surgery*	*Comments*
MAH	MTU+Sem	III B	No neoplasia	Biopsied	56	Stable residual disease
BC	TD	IV C L_3	No neoplasia	Biopsied	21	Stable residual disease
JMP	MTT+YS+Sem	II B	TD	100%	19	Disease-free
DA	YS+Sem	II B	No neoplasia	Biopsied	48	Stable residual disease
JP	MTU+YS+Sem	II A	TD	100%	3	Disease-free
DC	MTI+MTT	II C	TD	100%	29	Disease-free
BM	MTI	II C	TD (lap × 2)	Biopsied	53	Stable residual disease
MBH	MTI	II C	TD	100%	14	Disease-free
AI	MTI	IV B L_1	TD (thor)	Biopsied	30	Stable residual disease
PMA	MTI+YS	IV O L_1	TD (thor)	100%	57	Disease-free
AD	MTI+YS	II B	TD (1 focus MTI)	100%	6	Disease-free
CM	Sem	II C	PICC	100%	4	Disease-free
DS	MTU+Sem	II C	MTU	80%	8	Died of disease
DG	MTI	II B	MTI	100%	21	Disease-free
CG	MTU+Sem	II C	MTU+YS	Biopsied	2	Died of disease
JB	MTI+MTT	II C	MTI	100%	10	Disease-free
RP	MTI+YS	II B	MTI	100%	4	Disease-free
SH	MTI	IV O L_3	MTI (thor × 2)	Biopsied	54	Died of disease
PAM	MTU+YS	II B	MTU	100%	11	Lung and bone metastases. Now disease-free

lap = laparotomy thor = thoracotomy PICC = pancreatic islet cell carcinoma serious operative morbidity was a perforation of the third part of the duodenum (MBH). A primary repair was performed and the patient made an uneventful recovery.

Figures 1A, B and C show computerised axial tomograms of the region of the residual mass of patient MBH. Figures 1A and B show the abdominal mass enlarging, while in Figure 1C the mass is no longer present. The progress of patient DS can be followed in Figure 2. His mass was not completely removed and can be seen to enlarge post-operatively. He subsequently died of his disease.

Discussion

These operations can be difficult to perform. Some masses are easily removed *in toto* and others prove impossible to resect. Our confidence in dissecting the masses has improved with increased experience.

Our results demonstrate that if the histology shows no active malignancy, then the prognosis is excellent. It is our policy to follow carefully these patients without further treatment.

Residual malignant disease carries a much poorer outlook even after further aggressive treatment. Three of the nine patients in this group have died. The markers were elevated in two of the patients who died and complete excision was impossible in all three. In the remaining six patients, where complete excision was performed, only one patient has shown progression. He was successfully salvaged with further chemotherapy. Complete excision offers the best outlook for this group. These findings are similar to the results of Tait *et al.* (1984), but only 22% of their patients had residual malignancy compared with 47% of ours.

Unfortunately, there is no method of determining the nature of residual disease other than histology. As the composition of involved nodes has been shown to vary, simple biopsy may miss active disease. In our series of seven patients who were only biopsied, the histology accurately predicted the outcome and whether further treatment was indicated. One patient, however, had a single microscopic area of active disease. This causes concern as biopsy of residual nodes may well have missed his active disease. Indeed it could have been missed as a result of the pathologist's sampling error.

Our policy is to continue to debulk residual masses after induction chemotherapy and to attempt complete excision wherever possible. This takes into consideration the fact that 60% of patients will have an unnecessary operation (if the histology is benign) and that complete excision offers the best outlook for those with active malignancy. We have abandoned salvage surgery for any patient with raised tumour markers.

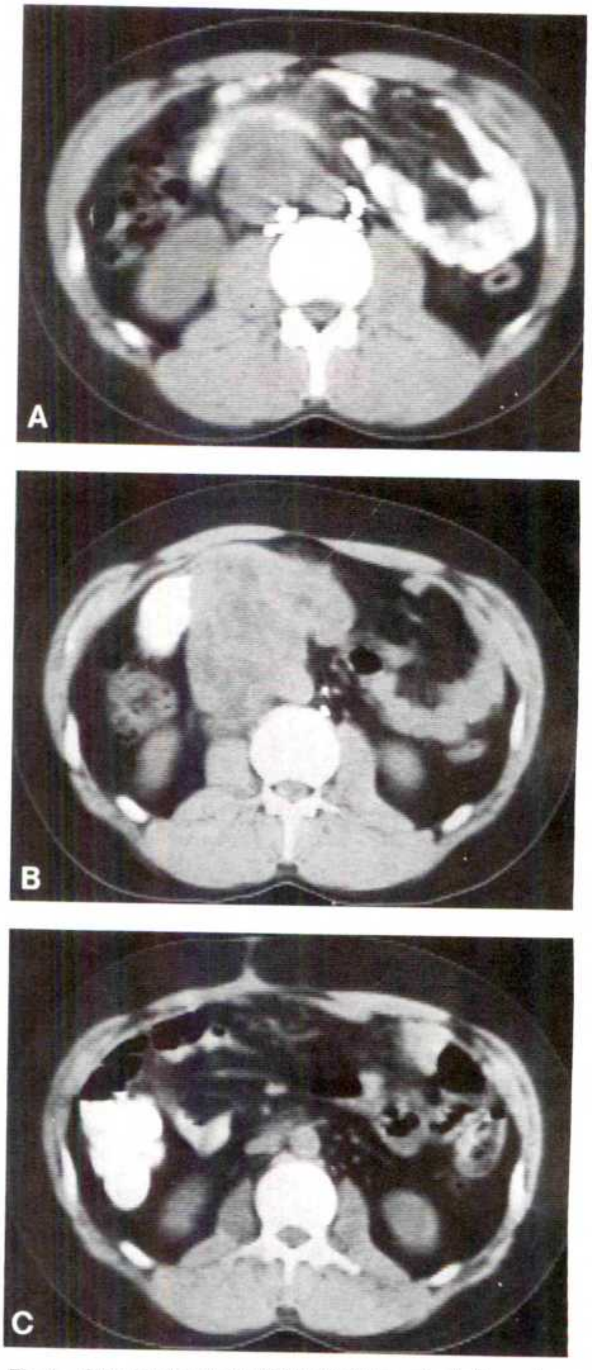

Fig. 1 CT scan of patient MBH. (A) 24 months before salvage surgery. (B) 1 month before salvage surgery. (C) 5 months after salvage surgery.

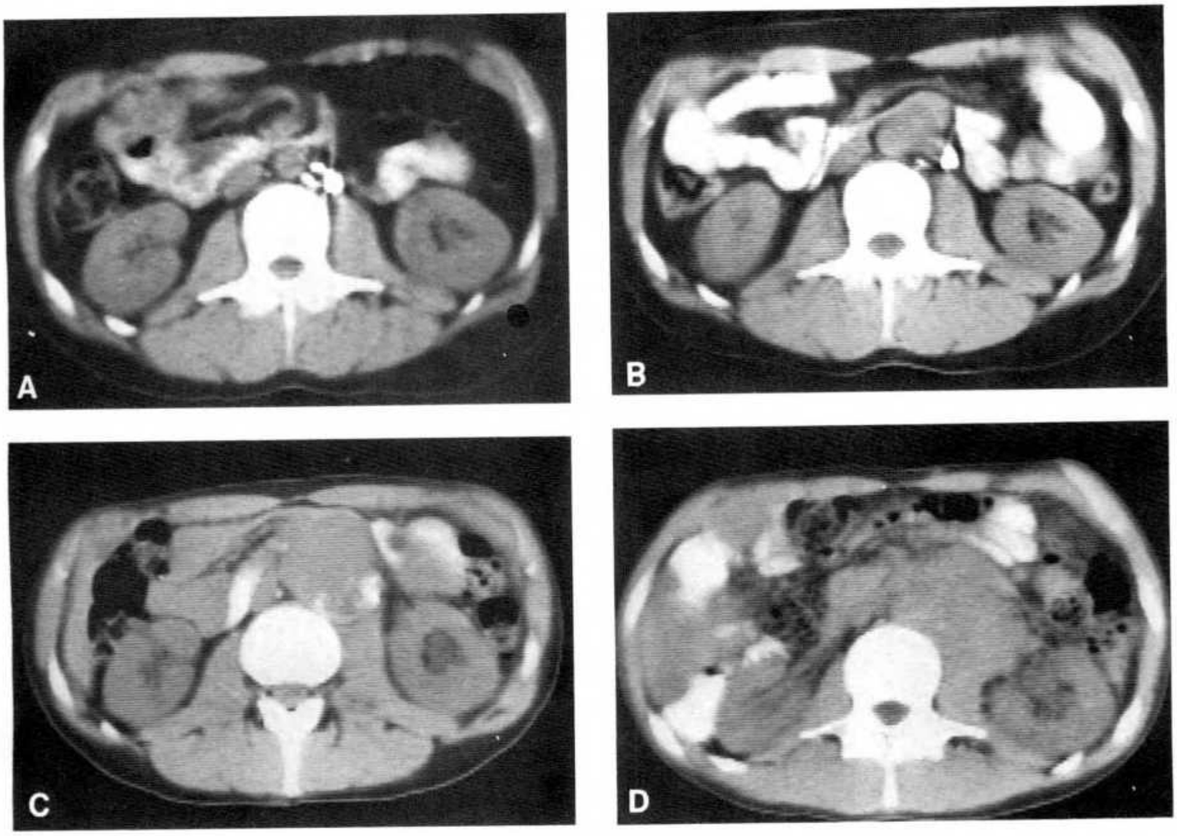

Fig. 2 CT scan of patient DS. (A) 13 months before salvage surgery. (B) 6 months before salvage surgery. (C) 1 month before salvage surgery. (D) 4 months after salvage surgery.

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Scope and Limitations of the MAGPI Hypospadias Repair

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Summary—Results and complications are reported in 67 boys who underwent a modified MAGPI procedure for hypospadias between 1981 and 1986. Excellent cosmetic and functional results were achieved in 91% of the patients. Some degree of chordee can be corrected by this procedure but severe degrees of chordee were associated with an increased complication rate.

Until the introduction of the meatal advancement and glanuloplasty (MAGPI) (Duckett, 1981) there was a tendency to avoid operations for glanular and coronal hypospadias because the procedures that were available often gave unreliable results and the benefits often did not outweigh the complications. Many patients with these minor degrees of hypospadias do have difficulty in directing the urinary stream and are embarrassed by the cosmetic appearance.

We have found the MAGPI operation most satisfactory and report our experience with a slightly modified procedure with particular reference to the management of patients with associated chordee.

Patients and Methods

Since 1981, 67 boys with distal hypospadias aged between 4 months and 15 years have been treated by a modified MAGPI procedure. The meatus was designated according to its site as glanular, coronal or subcoronal. The extent of the skin and/or fibrous chordee, as detected by artificial erection, was classified as nil, mild or moderate/severe (Table). The surgical procedure was essentially as described by Duckett (1981), but three 6/0 Vicryl sutures were used during the meatal advancement. Also an inverted "V" incision was made below the meatus instead of the transverse incision that was originally described (Fig.). This was closed with three or four 6/0 Vicryl sutures.

Correction of chordee was performed by excising the fibrous tissues of the corpora on each side of the urethra before the skin was reconstructed. If this resulted in a deficit of the ventral skin, the prepuce was split and brought round on to the ventral aspect as a single or double flap. A thin plastic infant feeding tube (4 or 6F) was left in the urethra overnight in all patients. The catheter was removed the following morning and they were discharged home. A few children had a more extensive dissection with skin transposition and then needed a silastic foam dressing as well as a catheter. Both of these were removed after 3 days. All boys were reviewed in out-patients 2 to 3 months later and the results assessed.

Table Distribution of the Location of the Meatus and the Complication Rate in Relationship to the Degree of Chordee

			Degree of associated chordee		
Location of meatus	*No*	*%*	*Nil*	*Mild*	*Moderate/severe*
Glanular	5	7	3	1	1
Coronal	60	90	33	19	8
Subcoronal	2	3	2	0	0
Total	67	100	38	20	9
Complication			2 (5.2%)	0	4 (44.4%)

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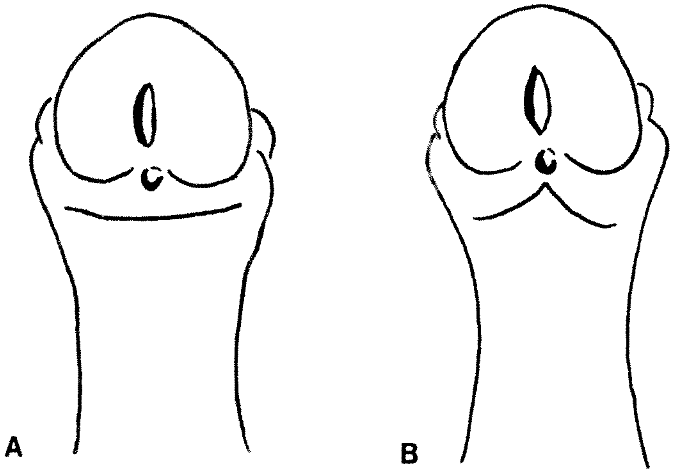

Figure (A) Incision below meatus as described by Duckett (1981). (B) Modified incision.

Results

Sixty-one of the 67 patients (91%) had excellent cosmetic and functional results. There were no fistulae, wound infections or skin sloughing. One patient developed a meatal stenosis which required a second operation. The meatus dropped back to some extent in four patients but further operation was deemed unnecessary. One boy had some residual chordee.

The complication rate was assessed in relation to the degree of original chordee (Table). In the 38 patients without chordee there was one with meatal stenosis and one in whom the meatus dropped back a little. In the 20 patients with mild chordee there were no complications, but in nine patients with moderate/severe chordee there were four complications. These four patients comprised three with some dropping back of the meatus and the patient with some residual chordee.

All boys voided satisfactorily when the catheter was removed either the next morning or when the foam dressing was taken off.

Discussion

The reported incidence of hypospadias is approximately 1:125 live male births (Sweet *et al.*, 1974), of whom 70% have a glanular, coronal or subcoronal meatus (Duckett, 1981). Previous operations using techniques described by Mathieu (1932), Devine and Horton (1977) and King (1981) were mostly effective but perhaps more liable to fistula formation and often gave a less acceptable cosmetic result than the MAGPI (Devine and Horton, 1977; Mills *et al.*, 1981; Wacksman, 1981; Woodard and Cleveland, 1982).

Previous reports of the MAGPI procedure have stressed the simplicity, cosmetic effectiveness and reliability of the operation (Livne *et al.*, 1984; Man *et al.*, 1984) and our experience confirms this view.

We have chosen to keep the children in hospital for 1 night with a thin plastic catheter draining the bladder to avoid the problem of the parents at home being concerned that the child may not void easily. If the operation has been more extensive, we found that the silastic dressing controlled the swelling most satisfactorily and on removal of the catheter no child has had difficulty in voiding.

Although we initially used Duckett's transverse incision below the meatus, we have now found that a "V" shaped incision tilts the glans to just the right degree, gives a more reliable closure with a less buried meatus, causes less bleeding during the dissection and, finally, facilitates the dissection of the skin from the proximal urethra (Figure).

Early in the series we probably brought round flaps of prepuce more often than was necessary and some boys appeared to have some excess ventral skin. We now only bring round skin, usually a single flap, when there is an obvious deficit.

Since 97% of the patients had a meatus that was glanular or coronal, the results have not been analysed with respect to the position of the meatus. We have, however, looked at the results and complications with respect to the degree of chordee. Twenty-five of the 29 patients with chordee had a good result. The four complications (three regressed meatuses and one residual chordee) occurred in the group with moderate/severe chordee, which is perhaps not unexpected, but within this group there remained over 50% with good results despite the moderate to severe chordee. There were no complications in the group with mild chordee. We believe that with careful selection it is possible to deal with *some* degree of chordee with the MAGPI procedure and this is borne out by the fact that over half of the boys with moderate to severe chordee have excellent results from this simple operation. We appreciate that this view is at variance with that of Gibbons (1985). We have not used corporal plication to correct chordee in conjunction with the standard MAGPI, as Livne *et al.* (1984) described, firstly because only one patient amongst 29 with chordee had a complication related to his chordee post-operatively; secondly, the long-term results of plication done in children are as yet unknown.

Our overall complication rate is 9%, which appears high for this operation, but we believe that minor degrees of meatal regression, as seen in this series, may have been ignored by others.

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Experience with Intracorporeal Injection of Papaverine and Duplex Ultrasound Scanning for Assessment of Arteriogenic Impotence

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Summary—We present our experience with the intracorporeal injection of papaverine and duplex sonography in the assessment of 47 patients with suspected vasculogenic impotence. Sonography and Doppler analysis were performed before and after the papaverine injection. The anatomy of the penis was easily seen. Flow in the deep arteries was obtained in most patients in both the flaccid and erect state. Patients with a good erectile response to papaverine injection had a larger increase in the inner diameter of the deep cavernosal artery than did those with a poor response. However, the percentage change in the diameter did not correlate with the degree of clinical response. Following injection, the systolic peak flow rates and diastolic minimum flow rates were higher in patients with some clinical response but only the increase in diastolic flow rates correlated in a step-wise fashion with the degree of clinical response.

This technique provides a method for the objective assessment of response to intracorporeal papaverine injection. Its potential as a diagnostic test will only be determined after normal values are established. At present it appears most useful in patients responding poorly to papaverine injection by indicating the possible area of vascular impairment and the direction for further evaluation.

Penile erection is a neuromuscular event involving relaxation of cavernosal smooth muscle, arterial dilatation and mechanical restriction of venous outflow (Newman *et al.*, 1964; Lue *et al.*, 1983). Penile anatomy and arterial blood flow through deep and dorsal arteries can be demonstrated by a duplex ultrasound scanner (Lue *et al.*, 1985). We assessed the response to intracorporeal papaverine injection by this method in a group of patients with suspected vasculogenic impotence and compared the results with the clinical assessment and other measurements of penile haemodynamics.

Patients and Methods

Forty-seven consecutive patients with suspected vasculogenic impotence (age range 41–71 years; average 54) presenting to the Erectile Dysfunction Unit, Ottawa Civic Hospital, were included in the study. They underwent a standard assessment consisting of history and physical examination, measurement of serum testosterone and blood glucose, penile brachial index (Abelson, 1975), penile plethysmography (Kedia, 1983) and snap gauge (Dacomed) nocturnal penile tumescence monitoring (Maatman *et al.*, 1986).

Duplex scans were performed using a real-time duplex mechanical sector scanner (ATL, Ultramark 8 TM) with an imaging frequency of 10 MHz and pulsed range-gated Doppler with a frequency of 5 MHz. High resolution real-time scanning revealed accurate details of the deep arteries and facilitated placement of the sample volume. The length of the sample volume was maintained at 1.5 mm. The frequency shift was transformed to velocity and quantified with a real-time gray-scale spectrum analyser using fast Fourier transform (FFT) analysis. The flow rates were angle corrected

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later using the Doppler equation. Hard copy was obtained of the resultant waveform, peak velocities and real-time images using a matrix camera.

The penis was scanned initially in the flaccid state to assess the corpora cavernosa and to evaluate the diameter of the deep arteries bilaterally. Measurements were made in the longitudinal direction with transverse images being used for orientation. Pulsed Doppler peak velocities and waveform analysis of each deep artery were then obtained with the angle of Doppler investigation as close to 60° as possible. The automatic angle correct was not used since the cursor obscured visualisation of the vessels. A rubber tourniquet was then placed about the base of the penis and 60 mg papaverine in 20 ml normal saline were injected into one corpus cavernosum using a 25 gauge needle. The tourniquet was removed after 5 min and the penis was assessed clinically for increase in girth and rigidity. The diameter and flow rates in the deep cavernosal arteries were then assessed near the base of the penis.

Results

The corpora cavernosa and the corpus spongiosum were easily seen in both longitudinal and transverse images (Fig. 1). These structures appeared uniform in echogenicity. One patient with Peyronie's disease had a plaque easily identified in relation to the dorsal neurovascular bundle. Ninety-four individual deep arteries (47 patients) were examined. One patient was excluded from the statistics because the hard copy was not adequate for review. Twelve deep arteries could not be visualised in the flaccid state and three could not be visualised after the injection. The deep arteries appeared centrally located in the transverse images of the corpora cavernosa and were easily seen by the echogenicity of the wall and often by their pulsation (Fig. 1). The pre-injection diameters of the deep arteries ranged from 0.3 to 1.1 mm. Five to 10 min after the papaverine injection, clinical erectile response was assessed and graded on a scale from 0 to 3 (Table 1).

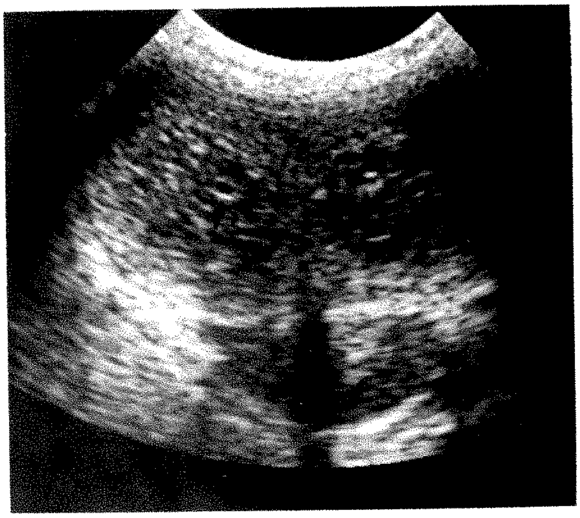
Fig. 1 Transverse scan of flaccid penis showing deep arteries (black arrows).

For the purpose of analysis, patients were divided into responders and non-responders. The pre- and post-injection diameters, cross-sectional areas and their means and standard deviations are shown in Table 2. While responders appeared to have a greater increase in diameter of the deep arteries following injection of papaverine, calculation of the increase as a percentage change in diameter indicated overlap amongst all but the lowest clinical response group (Table 3, Fig. 2). Five patients demonstrated diastolic flow before injection and 40 had measurable diastolic flow after injection. The mean peak flows in both systole and diastole showed a large range of standard deviation both before and after injection (Table 4). Mean systolic peak flows showed overlap in all but clinical response group 0, while minimum diastolic flows increased in a step-

Table 1 Clinical Response to Intracavernosal Injection of Papaverine

Group	*No. of patients*	*Response*
Non-responders	30	0 No change
		1 Moderate increase in size, slight rigidity
Responders	17	2 Marked increase in size, firm suboptimal rigidity
		3 Normal erection

Table 2 Mean Diameter and Cross-section Area of Deep Arteries in Response to Intracorporeal Injection of Papaverine

	Diameter (mm)	*Cross-section (mm^2)*	*Number of determinations*
Pre-injection	0.44 ± (0.23)	0.20 ± (0.16)	92
Post-injection	0.81 ± (0.25)	0.57 ± (0.36)	90

Table 3 Initial Diameter of Deep Arteries, Increment and Percentage Change with Intracorporeal Injection of Papaverine

Group	*Response group*	*Initial diameter (mm)*	*Increment (mm)*	*Percentage change*
Non-responders (30)	0	0.2–0.5	0.0–0.4	102
	1			283
Responders (17)	2	0.2–0.9	0.3–0.9	281
	3			243

wise fashion with the increase in clinical response (Table 4). Ten patients had pudendal angiography (Table 5). All patients in clinical response group 0 had diffuse disease of deep and dorsal arteries, while both patients in group 2 had normal penile vasculature angiographically.

In response group 1, four of five patients following papaverine injecton had a large increase in diameter of the deep arteries but sluggish flow rates and had proximal pudendal artery stenosis by angiography (Fig. 3). Six patients developed ecchymosis at the injection site. Nine patients developed erections exceeding 2 h in duration. Eight had successful detumescence with a single aspiration of a corpus cavernosum with a 21 gauge needle. One patient required two aspirations over a 4-h period.

Discussion

Impotence has been intensively investigated over the past decade, stimulated by the development of new diagnostic techniques and the evolution of multidisciplinary investigation units. This has led to the realisation that impotence is often a multifactorial problem and that in as many as 30 to 40% of

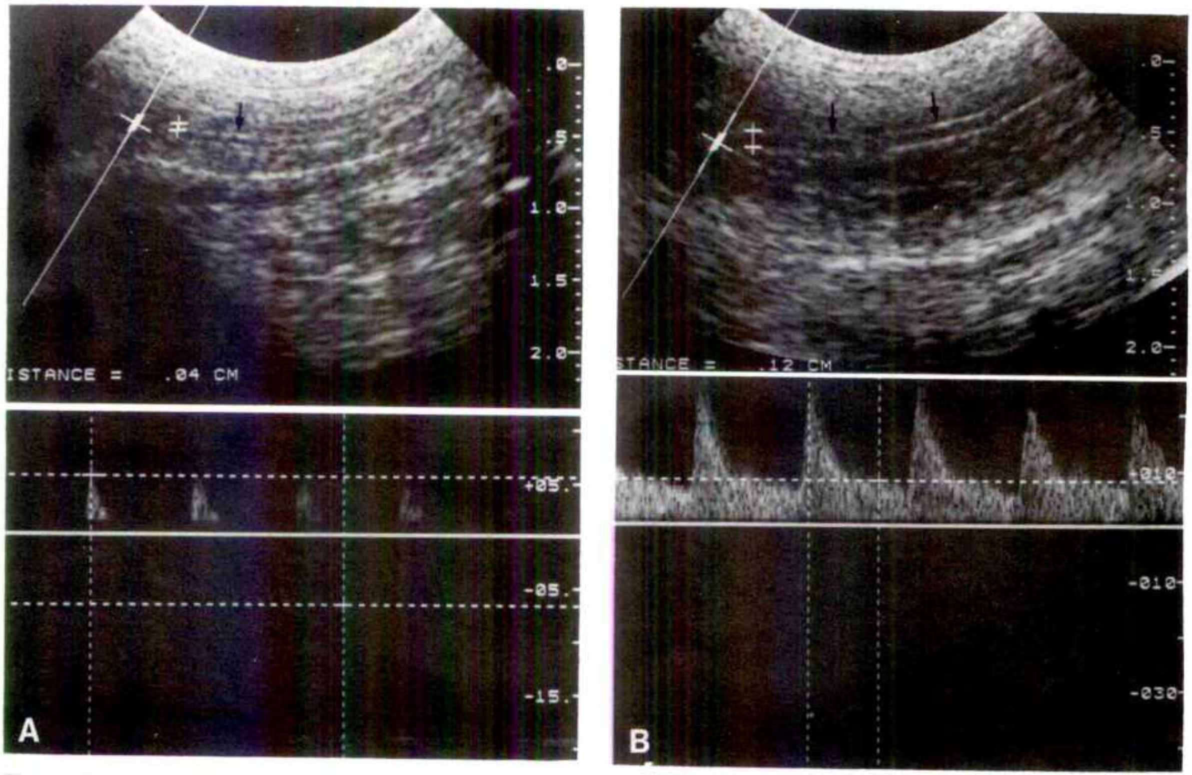

Fig. 2 Good response to papaverine injection. (A) In the flaccid state, longitudinal sonogram with the inner diameter of the deep arteries measuring 0.4 mm (black arrow) and peak systolic flow rate 6 cm/s. (B) Ten min after papaverine injection, the inner diameter of the deep artery increased to 1.2 mm (black arrows) and peak systolic flow rate to 20 cm/s with good penile tumescence. Note the easily demonstrable diastolic flow.

Table 4 Mean Flow Rates in Deep Arteries with Injection of Papaverine and Correlation with Clinical Response

	Mean (corrected) peak flow (cm/s)		*Clinical response group*	*Mean (corrected) systolic peak flow (cm/s)*	*Mean (corrected) minimum diastolic flow (cm/s)*
	Systole	*Diastole*			
Before injection	9.9 ± (9.3)	0.34 ± (1.5)	0	4.5	4.0
			1	21.0	8.2
After injection	26.8 ± (17.2)	7.7 ± (5.6)	2	13.0	11.3
			3	21.0	19.3

Table 5 Pudendal Angiography Correlated with Clinical Response to Intracorporeal Papaverine and Duplex Scanning

No. of patients	*Clinical response*		*% Change in diameter*		*Mean systolic peak flow (cm/s)*		*Diffuse deep vessel disease*	*Prox. Pud. Obstr.*	*Pud. Norm.*
	Group	*No.*	*Subset*	*Group*	*Subset*	*Group*			
10	0	3	100	102	4.2	4.5	3	0	0
	1	5	281	283	8.0	21.0	1	4	0
	2	2	274	281	12.0	13.0	0	0	2

cases some organic factor is involved (Federman, 1982; Collins *et al.*, 1983). History and physical examination may identify some causes such as Peyronie's disease and may indicate possible aetiological areas for further investigation. In most instances, clinical impressions must be substantiated by objective diagnostic tests (Blaivis *et al.*, 1980). Suspected venous problems may be assessed by cavernosography (Jevtich and Maxwell, 1983). Arterial problems are usually assessed by indirect tests. The penile brachial index has been widely used either as originally described (Abelson, 1975) or with variations (Velcek *et al.*, 1980). Penile plethysmography has also been recommended (Kedia, 1983). However, clinical assessment and indirect tests may yield false impressions of vascular insufficiency (Blaivis *et al.*, 1980).

The demonstration that intracorporeal injection of papaverine produced erections in normally potent men (Virag *et al.*, 1984) indicated that it might be a useful functional test for the assessment of vasculogenic impotence. Lue *et al.* (1985) showed the feasibility of combining intracorporeal papaverine injection with penile assessment by duplex ultrasound scanning. This technique provides an objective method of assessing response to intracorporeal papaverine injection. The procedure proved to be rather tedious initially (each lasting approximately 45 min). Although duplex scanning facilitates the localisation of the sample volume,

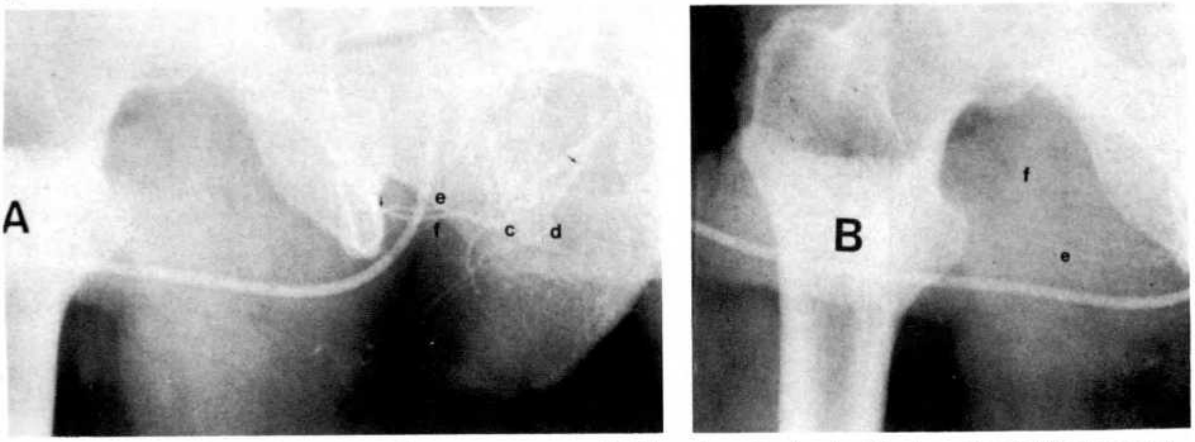

Fig. 3 Pudendal angiogram in patient with poor tumescence. (A) Sites of proximal pudendal artery stenosis (black arrows). Arteries: internal pudendal (c), perineal (d), deep (e), dorsal (f). (B) Delayed visualisation of deep (e) and dorsal (f) arteries distal to sites of stenosis in pudendal artery.

stabilisation of the sample volume long enough to obtain hard copy results proved difficult. Ideally, four well-trained hands are necessary to complete an examination. A firm erection following injection of papaverine was associated with the greatest increase in deep artery diameter and higher flow rates, as in clinical response group 3.

There is increasing evidence (Buvat *et al.*, 1986) that a firm erection following papaverine injection indicates the absence of vasculogenic impotence, making objective evaluation of this response redundant. An equivocal clinical response to papaverine injection yields little information about penile haemodynamics (Virag *et al.*, 1984; Buvat *et al.*, 1986). This technique has potential as an objective evaluation of suboptimal clinical response to papaverine injection. Arteriogenic impotence can be implicated after papaverine injection when there is little or no arterial dilatation, sluggish flow and lack of clinical response, as in response group 0. It is noteworthy that several patients with sluggish flow but good dilatation of deep arteries following papaverine injection had proximal pudendal artery obstruction with relatively normal dorsal and deep penile vessels angiographically. These patients are potential candidates for penile revascularisation and could thus be identified by this technique as a group to be assessed by more invasive pudendal angiography. Patients with short-lived erections associated with normal vessel dilatation and high flow rates might have a venous problem and be candidates for further assessment by cavernosography.

More studies are needed to determine normal values for deep artery size, dilatability and flow rates. Normal values will have to reflect variation in penile size as well as degree of erection. Our data were assessed in relation to a subjective clinical categorisation of response to papaverine injection. Large standard variations in vessel diameter and flow rates produced overlapping values for most clinical categories. With a knowledge of normal values, a comparison of deep artery size and flow rates with other measurable penile variables may reflect more accurately the response to intracorporeal papaverine. Vessel size may be better evaluated by comparison with diameter, cross-sectional area or volume of the corpus cavernosum. Total volume of flow per min in the deep arteries or time averaging over a series of heart beats yielding a pulsatility index might reflect deep arterial flow more accurately. Such data may correlate better with clinical response and reveal more subtle abnormalities of arterial flow to which more precise diagnostic and/or therapeutic measures might be applied.

In conclusion, this technique permits a direct objective assessment of papaverine-induced erectile response, providing several measurements for analysis. While more clinical experience is required to define normal values, it has the potential to be a useful complement to diagnostic tests currently available and may develop into the primary radiological assessment for arteriogenic impotence.

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Case Reports

Analgesic Nephropathy Complicated by Transitional Cell Carcinoma of the Renal Pelvis

C. R. CHAPPLE, *Department of Urology*, J. NEWMAN, *Department of Histopathology*, J. M. O'BRIEN and J. CONSIDINE, *Department of Urology, East Birmingham Hospital, Birmingham*

Following a report by Hultengren *et al.* (1965), it has been suggested that phenacetin abuse predisposes to urothelial neoplasia. Any part of the urothelium may be affected, but most striking is the high incidence of renal pelvic neoplasia, with over 100 recorded cases in the literature. The first fully documented case from Great Britain is now reported.

Case Report

A 46-year-old female presented with an attack of left renal colic and subsequently passed two pieces of brown tissue *per urethram*. Histological analysis proved these to be necrotic renal papillae. She had regularly consumed analgesics for 24 years, with an estimated ingestion of 9 kg aspirin and 9 kg phenacetin.

At the age of 63 she complained of right loin pain with associated macroscopic haematuria. An intravenous urogram demonstrated a filling defect in the right renal pelvis, confirmed by retrograde pyelography (Fig.). A right nephro-ureterectomy was performed. A multifocal papillary transitional cell tumour was present at the pelviureteric junction. Histological examination revealed this to be a high grade tumour; there was adjacent carcinoma *in situ* and urothelial dysplasia. She remains free of recurrent tumour 15 months later.

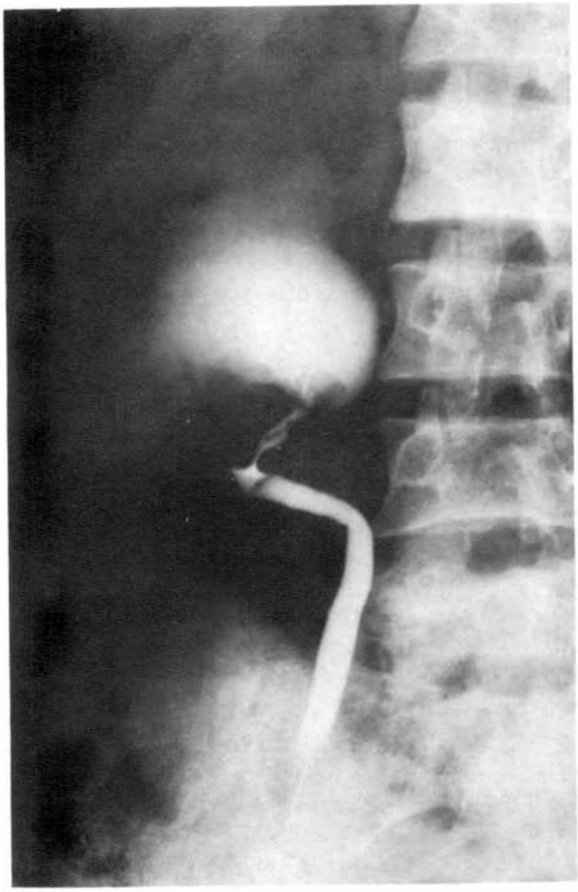

Fig. Right retrograde pyelogram. The renal pelvis is dilated. A filling defect is present in the upper ureter, producing an "apple-core" effect.

Comment

Patients with analgesic nephropathy have widespread urothelial dysplasia which predisposes to neoplasia (Blohme and Johansson, 1981). They need careful monitoring and urine cytology has been found to be particularly useful. When neoplasia develops their prognosis is poor. Recent epidemiological and experimental work has challenged the importance of phenacetin (Prescott, 1982). Thus the aetiology and pathogenesis of urothelial neoplasia complicating analgesic nephropathy remain unknown.

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Renal Abscess with Gas Formation Secondary to Acute Appendicitis

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Gas-forming infections of the kidney are rare and dangerous (Costas, 1972). An unusual case with a satisfactory outcome is reported.

Case Report

A previously fit 72-year-old female presented with a 3-week history of anorexia and confusion. She was dehydrated and drowsy and had a right-sided abdominal mass. Plain X-rays and an intravenous urogram showed a gas-containing abscess involving the right kidney and also gas in the bladder (Fig. 1).

Marked hyperglycaemia and dehydration were corrected with insulin, intravenous fluids and antibiotics. The right kidney was then explored and a large abscess cavity drained. Pure *Escherichia coli* was grown from the pus. A fistulogram performed via the drain 10 days later showed a communication with the right ureter (Fig. 2).

At right nephrectomy 4 months later, the renal pelvis was found to be densely adherent to the right colon and the appendix. An appendicectomy was therefore also performed. Histology showed chronic pyelonephritis and a renal abscess cavity communicating with the remains of the appendix.

The patient made a full recovery and became normoglycaemic on no medication for the first time since the illness began.

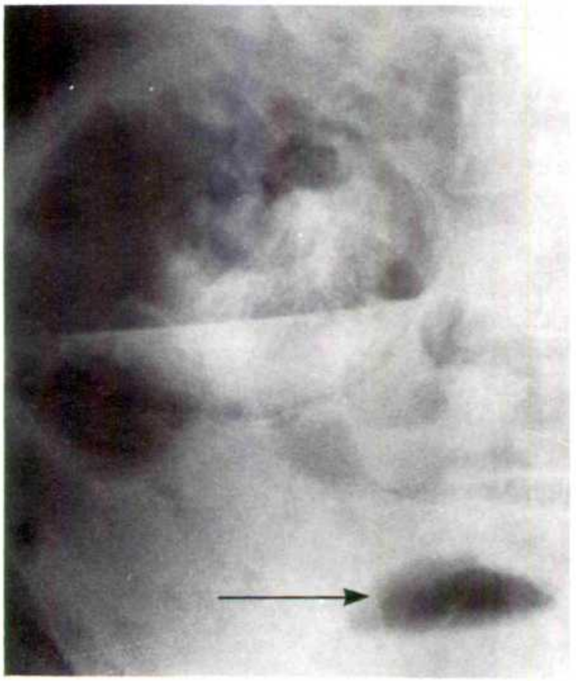

Fig. 1 Plain erect abdominal X-ray showing abscess with gas/fluid level involving the right kidney and gas in the bladder (arrow).

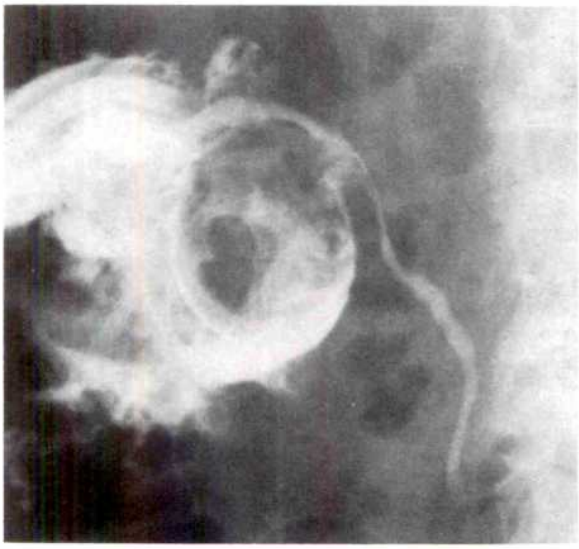

Fig. 2 Fistulogram via drain showing communication of cavity with the right ureter.

Comment

Gas-producing infections of the kidney occur in patients with diabetes mellitus, obstructive uropathy or a combination of the two (Costas, 1972). This patient was a latent diabetic whose diabetic state was probably provoked by appendicitis. It has been suggested that gas formation in such cases is due to fermentation of excess glucose by *Escherichia coli* (Gillies and Flocks, 1941). Despite apparently adequate drainage of the abscess it was only after nephrectomy that the diabetic state resolved completely.

Acknowledgements

I thank Dr P. F. O'Sullivan, Mr J. M. Powley and Mr J. P. Ward for permission to report this case.

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Recurrent Inversion of the Urinary Bladder

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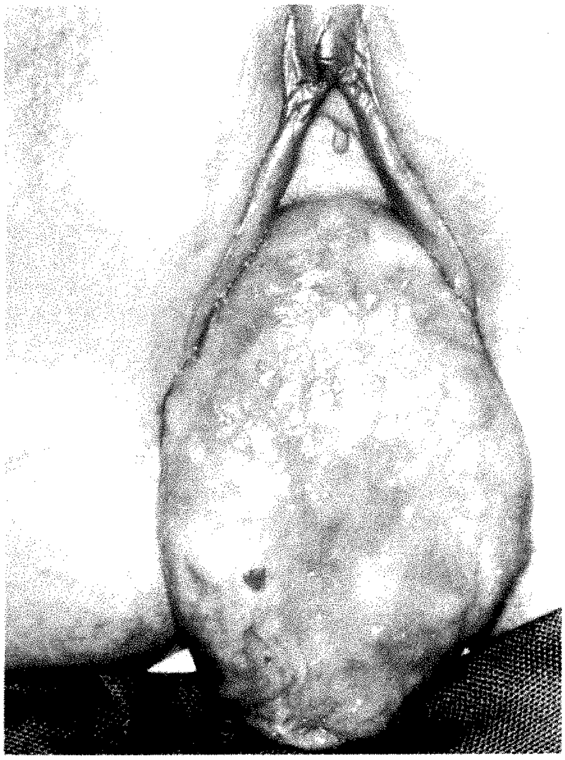
Case Report

A 64-year-old multiparous female was admitted with a history of bleeding from a perineal mass and incontinence of urine of 2 days' duration. She stated that this had occurred on several occasions over the last 5 years and on every occasion she was able to reduce the mass herself. There was no history of previous hospitalisation. On examination she was frail, mildly dehydrated and was not in pain. There was no systemic abnormality. On inspection of the perineum there was a rounded reddish mass protruding through the patulous urethral meatus (Fig.). On the surface of the mass there were a few haemorrhagic spots and clear urine was seen effluxing out of two slit-like openings on the mass. There was no uterine prolapse. A diagnosis of complete bladder inversion was made. She was sedated in the ward and the mass was easily reduced. Results of laboratory investigations were: haemoglobin 9.5 g/dl, blood urea 18.4 μmol/l, serum creatinine 230 mmol/l. Intravenous urography showed bilateral hydronephrosis. In view of the weak perineal musculature, hydronephrosis and deteriorating renal function, corrective surgery was undertaken. Colposuspension combined with a vesicorectus hitch was performed electively. Post-operative recovery was uneventful and on discharge from hospital she was continent of urine. The BUN and serum creatinine level subsequently improved. She defaulted from follow-up and attempts to get her to return for repeat IVU were unsuccessful.



Comment

Inversion of the bladder alone without associated procidentia is an extremely rare condition. Only a single case report of "acute" inversion (Thavarasah and Attygalle, 1978) could be found in the literature and there does not appear to be any case of recurrent inversion. Owing to the fact that the mass was previously easily reducible and not causing much pain, the patient had never sought medical treatment. Bleeding and irreducibility had prompted the present admission. Diagnosis did not present a problem, though at first glance the protruding mass could be confused with a third degree uterine prolapse. Multiparity and general debility may account for the weak pelvic musculature but it is not clear why there was no associated procidentia. Recurrent inversion had resulted in chronic bilateral hydronephrosis and impaired renal function. Surgical intervention was necessary and colposuspension with fixation of the bladder to the rectus sheath anteriorly seemed to be the most logical treatment.

Acknowledgement

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Unusual Foreign Body in the Bladder

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Case Report

A 60-year-old female presented with a 6-month history of complaints suggestive of a vesical calculus. She had received a hip prosthesis 6 years earlier for a fracture of the neck of the right femur.

Abdominal examination revealed no abnormality but on rectal examination a hard, round, mobile mass measuring 6 to 7 cm was felt anteriorly. X-ray of the pelvis revealed a dislocated hip prosthesis lying centrally (Fig.). At cystoscopy the metallic prosthesis was found to be lying freely inside the bladder and it was removed by suprapubic cystotomy. A fistulous tract, which extended from the bladder inferolaterally towards the right acetabulum and which contained the stem of the prosthesis, was excised. Recovery was uneventful.

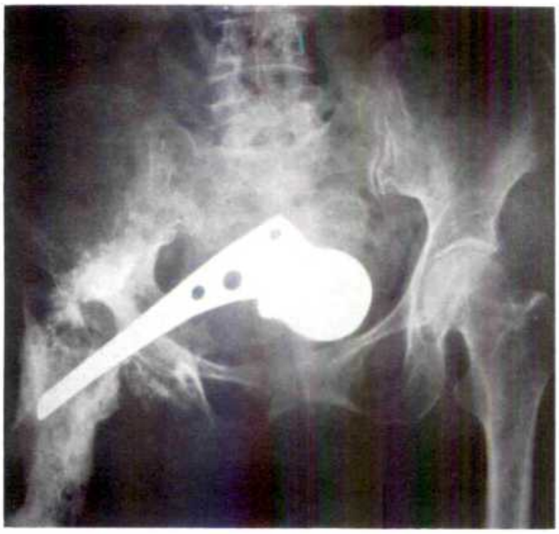

Fig. Radiograph showing metallic hip prosthesis.

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Paraffinoma of the Ureter

J. KELLEHER, S. WILSON and R. O'N. WITHEROW, *Department of Urology, St Mary's Hospital, London*

Paraffinoma is a well recognised complication following instillation of paraffin into the tissues (Campbell and Henderson, 1973) but its deleterious effects have not been previously reported in the urinary tract.

Case Report

A 51-year-old man presented 4 years after treatment at another hospital for right ureteric colic. Since that time he had suffered from recurring pain in the right loin.

An IVU revealed a non-functioning right kidney. No stone was seen on the control film. A DMSA scan showed less than 10% function on the right side. A right ascending ureterogram revealed a 2-cm long tapering stricture 3 cm from the right ureteric orifice, through which contrast passed into the proximal dilated ureter. In view of the poor renal function and uncertainty of diagnosis a right nephroureterectomy was performed. Macroscopically the lower ureter appeared fibrosed and the kidney was hydronephrotic.

This unusual appearance prompted inquiries as to exactly what treatment he had received 4 years previously. Apparently a small ureteric calculus had impacted at the right ureterovesical junction and endoscopic removal was attempted with the Dormia basket. Several attempts had proved unsuccessful, but before abandoning the procedure liquid paraffin had been injected into the right ureter via a retrograde catheter "to ease the passage of the stone".

Histological sections of the ureter showed fibrosis in the wall, both in the intramural and extravesical portions, and in the adjacent adipose tissue and detrusor muscle (Fig.). There were numerous spaces of varying size bordered by giant cells of a foreign body type. Frozen sections stained with oil red showed the spaces to be filled with an oily substance consistent with liquid paraffin.

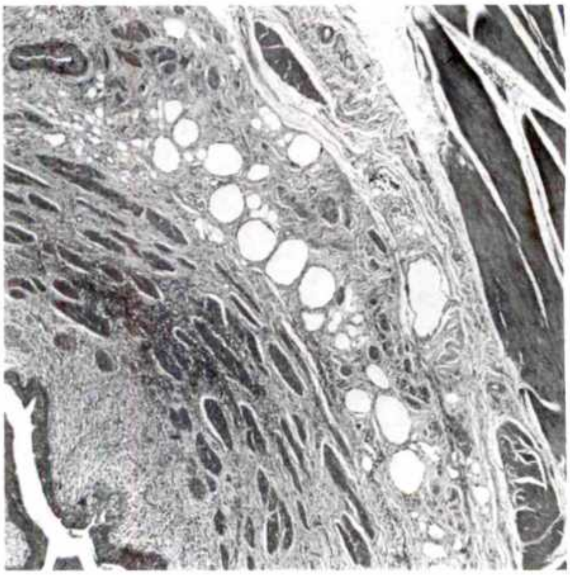

Fig. Histological section showing fibrosis in the ureteric wall and periureteric tissues, with spaces containing liquid paraffin. (×15).

Comment

The use of a mixture of olive oil and local anaesthetic is well documented as a lubricant to aid the passage of a ureteric stone (Cromwell, 1921). Its efficacy is doubtful. The instillation of paraffin into the ureter has not been described previously, but when injected into tissues such as the breast, face or genitalia it leads to the formation of the classical paraffinoma (Campbell and Henderson, 1973). Even instilling paraffin intra-abdominally in the hope of preventing adhesions causes this lesion (Kastilabros, 1973) and it has been described following dilatation of the cervix where the instruments were lubricated with paraffin (Campbell and Henderson, 1973). The typical appearance of the paraffinoma in this case suggests that the stricture did not follow the use of the basket alone. We recommend that liquid paraffin should not be injected into any part of the urinary tract or used as a lubricant for endoscopic procedures.

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Requests for reprints to: R. O'N. Witherow, St. Mary's Hospital, London W2.

An Unusual Retroperitoneal Seminoma

R. R. JEFFREY, D. J. L. MALONEY and K. M. GRIGOR,
Department of Pathology, University of Edinburgh, Edinburgh

Case Report

A male Caucasian first presented in 1967 at the age of 24 with a 3-month history of intermittent left loin and back pain. On examination he had a mass in the left hypochondrium which was visible on plain abdominal radiography. An intravenous urogram at that time demonstrated a non-functioning left kidney and retrograde pyelography showed lateral displacement of the ureter. Laparotomy was performed and the patient was found to have a large retroperitoneal tumour which was biopsied. The pathology reports initially suggested a "reticulum cell sarcoma" (Fig. 1). He received "palliative" wide-field radiotherapy to the abdomen, excluding the testes.

After 14 years, during which time he had remained well, he was again seen following an episode of presumed orchitis which appeared to respond to antibiotics. On examination he had a swollen hard left testis. His serum lactate dehydrogenase was markedly elevated at 6289 iu/ml and an intravenous urogram showed no obstruction to drainage from the left kidney. He underwent inguinal orchiectomy, histopathological examination showing classical seminoma with coexisting carcinoma *in situ* (Fig. 2). Review of the pathology of his original retroperitoneal tumour revealed a similar morphological pattern and the original diagnosis was changed to seminoma. He required no further treatment and is well 1 year later with no demonstrable recurrence on chest X-ray or CAT scan of chest and abdomen. His serum lactate dehydrogenase returned to normal post-operatively and has remained normal.

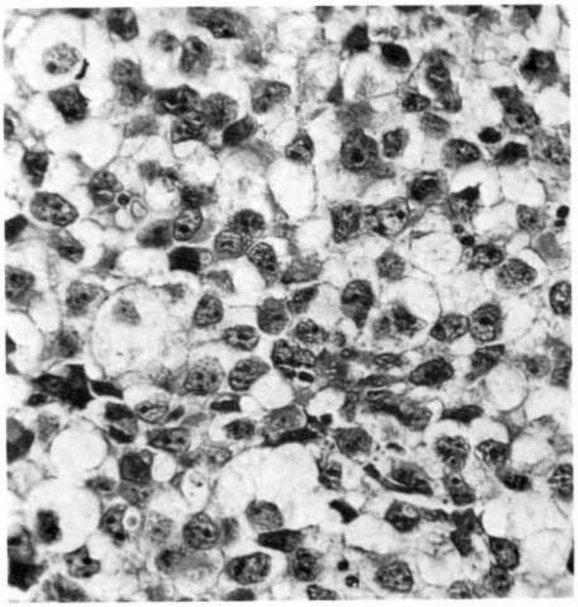

Fig. 1 Retroperitoneal seminoma, originally thought to be a "reticulum cell sarcoma". (H and E × 320).

Comment

Seminoma may present as metastatic tumour mimicking a lymphoreticular neoplasm or so-called "reticulum cell sarcoma", the correct diagnosis only becoming apparent after subsequent discovery of a testicular swelling (Abell *et al.*, 1965). In the present case, the favourable response of the retroperitoneal tumour to radiotherapy lends support to the change of diagnosis to seminoma.

The presence of carcinoma *in situ* in the seminiferous tubules adjacent to the testicular seminoma (Fig. 2) confirmed this to be a primary testicular neoplasm. While the retroperitoneal seminoma may have been a metastatic deposit from the

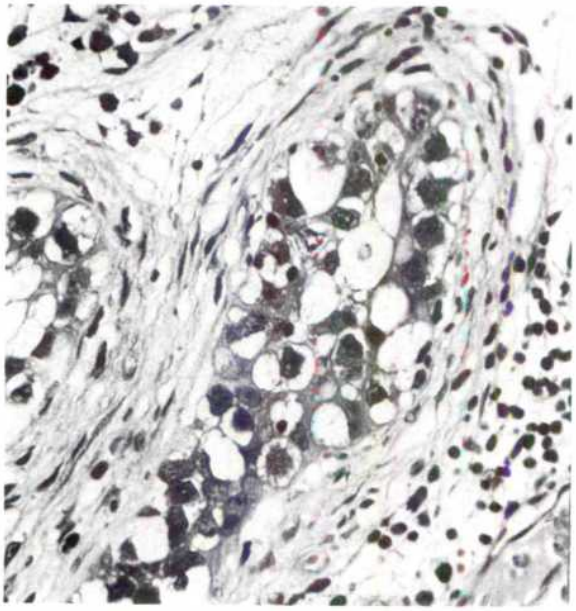

Fig. 2 Seminiferous tubules adjacent to testicular seminoma showing carcinoma *in situ*. (H and E × 320).

testicular tumour which had remained occult for 14 years, the retroperitoneum is a recognised site for the development of primary germ cell tumours (Phalakornkule and Woodruff, 1964; Abell *et al.*, 1965; Wegenke *et al.*, 1977) and therefore the alternative suggestion of two sequential primary seminomas developing at different sites must be considered. Whether this case represents a single tumour with prolonged occult interval, or sequential double primaries, cannot at present be resolved.

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Wegenke, J. D., Chuprevich, T. W. and Nilsson, T. E. G. (1977). Retroperitoneal seminoma. *J. Urol.*, **117**, 262–263.

Requests for reprints to: K. M. Grigor, Department of Pathology, University Medical School, Teviot Place, Edinburgh.

Intermittent Hydronephrosis due to Transitional Cell Carcinoma of the Renal Pelvis

P. J. ENGLISH, G. WILLIAMS and R. N. P. CARROLL,
Departments of Urology and Pathology, Royal Infirmary, Manchester

We report an unusual case of intermittent hydronephrosis where the cause was thought to be a transitional cell carcinoma of the renal pelvis.

Case Report

A 49-year-old woman presented with a 6-month history of intermittent left loin pain. There was no relationship of the pain to fluid consumption or any history of haematuria. Physical examination was normal and no abnormality was detected on urine analysis or the initial IVU.

Five weeks later, a diuretic renogram at the time of pain demonstrated an obstructed left kidney. A further IVU shortly after the pain had subsided showed only minimal distension of the left renal pelvis (Fig. 1) but an obvious hydronephrosis was seen to develop after intravenous frusemide (Fig. 2).

At the time of surgery the renal pelvis was not distended and felt normal. An Anderson-Hynes pyeloplasty was performed, but examination of the resected specimen showed it to incorporate a mucosal, villous tumour approximately 1.5 cm in diameter, situated in the pelvis immediately adjacent to the pelviureteric junction. Histological study confirmed a grade I transitional cell carcinoma confined to the mucosa. The patient subsequently underwent a left nephroureterectomy.

Comment

The usual cause of intermittent hydronephrosis is an idiopathic obstruction of the pelviureteric junction. In one reported case a benign ureteric polyp was thought to be responsible (Thorup *et al.*, 1981) but we are unaware of any previous report attributing the condition to a transitional cell carcinoma of the renal pelvis. Intermittent impaction of the head

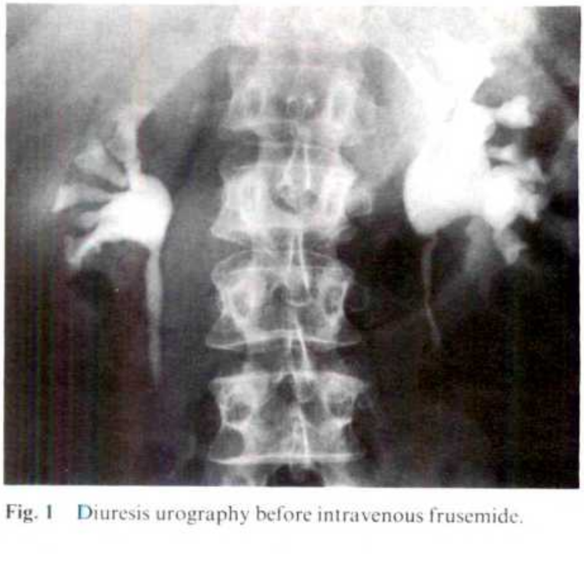

Fig. 1 Diuresis urography before intravenous frusemide.

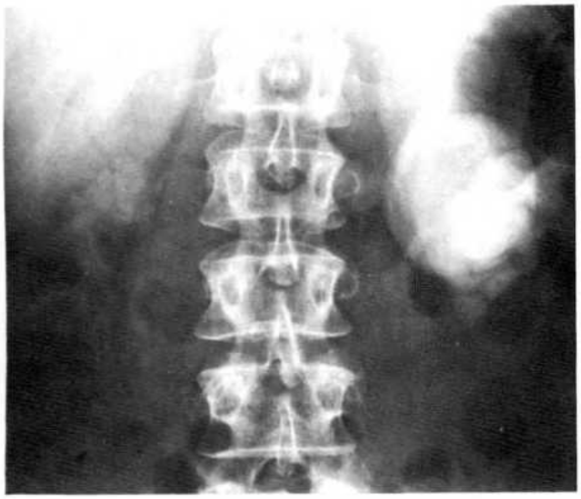

Fig. 2 Diuresis renography 15 min after intravenous frusemide.

of the tumour at the pelviureteric junction was the probable mechanism of obstruction in the present case.

Reference

Thorup, J., Pedersen, P. V. and Clausen, N. (1981). Benign ureteral polyp as a cause of intermittent hydronephrosis. *Journal of Urology*, **126**, 796-797.

Requests for reprints to: R. N. P. Carroll, Department of Urology, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL.

Giant Renal Calculus

T. S. MAHANT, D. C. MERWAHA, R. R. GUPTA and S. KAPOOR, *Department of Surgery, Himachal Pradesh Medical College, Simla, India*

Renal calculi weighing more than 100 g are rare, since most stones cause arrest of renal function before they reach such proportions. We report a giant renal calculus weighing 2260 g; to our knowledge this is the largest reported.

Case Report

A 54-year-old man was admitted with a gradually progressing lump in the left upper abdomen of 12 years' duration. He had no urinary or bowel symptoms. Blood pressure was normal. Examination revealed a large lump on the left side of the abdomen, hard in the centre and cystic elsewhere, descending towards the pelvis. Routine urine and blood examination were normal. Plain X-ray showed a large balloon-shaped calcified shadow in the left renal area and intravenous urography showed a non-functioning left kidney (Fig.). A left nephrectomy was performed. Section of the specimen revealed a single large calculus in the pelvis of the kidney which weighed 2260 g. Post-operative recovery was uneventful.

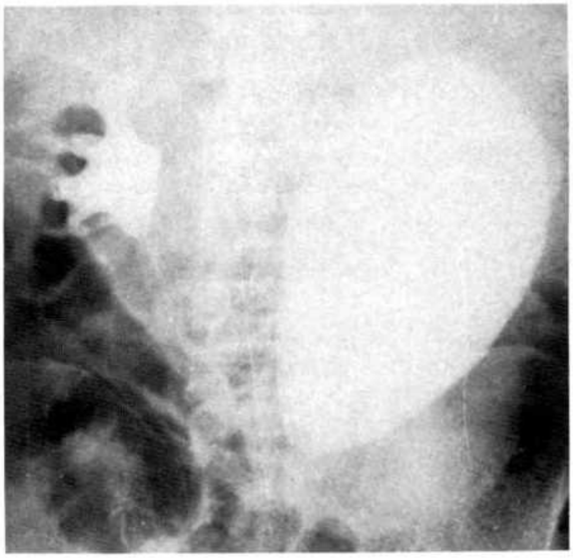

Fig. Intravenous urography showing normal right ureter and kidney, no excretion of dye on the left side. Large radio-opaque density in left renal region.

Comment

Renal calculi do not become very large when obstruction is present, because impairment of function decreases the material necessary for their growth. On the other hand, stones which do not cause obstruction may reach an incredible size without causing many symptoms. The largest stone reported before the present one weighed 2100 g (Landes, 1953; Misgar *et al.*, 1962; Dumbadze *et al.*, 1979).

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Requests for reprints to: T. S. Mahant, Department of Surgery, Himachal Pradesh Medical College, Simla-171001, India.

Renal Carcinoma with Hypercoagulability

D. C. RAYNER, G. N. HOAG and T. A. KHAN, *Departments of Pathology and Surgery, Health Sciences Centre, Winnipeg, Canada*

Case Report

A 53-year-old, insulin-dependent, diabetic man was referred to hospital with acute abdominal pain. Physical and radiographic findings indicated ileus compatible with ischaemic bowel; at laparotomy a 150-cm segment of infarcted ileum was resected. Pathological examination showed mesenteric venous thromboses.

There was moderate thrombocytosis (mean 580×10^9/l, range $330\text{-}851 \times 10^9$/l) which persisted during his stay in hospital. Marked initial leukocytosis (45.2×10^9/l) diminished in the post-operative period but remained in the range of 12.1 to 21.1×10^9/l. Initial prolongation of the prothrombin time (15 s, 40% of control activity) improved with parenteral vitamin K; however, factor assays showed elevation of Factor VIII coagulant activity (230% of control).

Fever developed on his eighteenth day in hospital. *Klebsiella pneumoniae* was cultured from the abdominal wound but fever persisted despite tobramycin and clindamycin. He died on his twenty-third day in hospital after an abrupt hypotensive episode. At necropsy there was occlusive thrombosis of the superior mesenteric, portal and splenic veins and splenic artery thrombosis with massive splenic infarction. Thromboemboli of indeterminate source occluded both pulmonary arteries. A 7-cm renal carcinoma of typical "clear cell" histology was present in the lower pole of the right kidney with no extrarenal or renal vein invasion and no evidence of metastatic disease. Histological sections of the venous and arterial thrombi and pulmonary thromboemboli were free of tumour.

Comment

Thrombotic and embolic complications of renal carcinoma may follow invasion of the renal vein and inferior vena cava (Levine and Airhart, 1977) but hypercoagulability with distant thrombosis, in this case mesenteric venous thrombosis, represents an exceptional mode of presentation. Hypercoagulability is a common presentation or complication of other malignant tumours and is believed to involve multiple pathogenic mechanisms, including elevated levels of coagulation factors and thrombocytosis (Kies and Kwaan, 1982). Moreover, a substantial minority of patients with localised or disseminated renal carcinoma have secondary thrombocytosis and leukocytosis, which may mimic primary haematological disease (von Knorring *et al.*, 1981).

Renal carcinoma may present with hypercoagulability and distant thrombotic manifestations.

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Requests for reprints to: D. C. Rayner, Department of Immunology, The Middlesex Hospital Medical School, Arthur Stanley House, 40-50 Tottenham Street, London W1P 9PG.

British Journal of Urology (1987), 59, 97-98

Point of Technique

Simulated Testis Using Vascularised Autogenous Tissue

S PARKASH, *Department of Surgery, Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry, India*

The testis often has to be removed and it is usually replaced by a prosthesis. Silastic prostheses of suitable consistency and shape appear to be the most popular (Prentiss and Sorenson, 1973), but they are expensive and not readily available in developing countries.

Simulated testes have been constructed in seven patients over the last 3 years. All were adults, ranging in age from 24 to 64 years; five were less than 31 years old. Two had a chronic haematocele and calcification with complete atrophy of the testis, complicted by infection in one case. Five patients had undescended testes at various levels (Table).

In case 2, the rectus abdominis (outer part) with overlying sheath was turned down and the upper end folded on itself to form a suitable shape. Ipsilateral inferior rectus abdominis de-epidermised myocutaneous flaps were used in cases 1 and 5 (Parkash and Palepu, 1983). In case 4 a dermofat flap based on a rectus abdominis pedicle (Taylor *et al*, 1983) was used to replace an infected haematocele (Fig. 1).

Dartos-based scrotal flaps were used in three patients. Case 3 had a large right indirect inguinoscrotal hernia and a left undescended testis. A flap of scrotal skin from the opposite side was de-epidermised, divided all round to the level of the dartos, and rolled to make a testis. A contralateral flap (posterior) was fashioned and rolled in. A bipedicled flap was used in case 6, who underwent orchiectomy for almost absent undescended testes (Fig. 2). Case 7 had a large haematocele and advanced carcinoma of the penis extending to the shaft. The testis was atrophic and orchiectomy was carried out. The penis was lengthened by dividing the suspensory ligaments and an amputation was performed. One large (right) and a small (left) anterolateral scrotal flap covered the penis and a

Table Details of Patients

No	*Age (years)*	*Disease*	*Technique*	*Result*	*Remarks*
1	24	Left undescended testis	Ipsilateral inferior RA MC flap De-epidermised	Normal feel, symmetrical size	No defect abdominal wall 2 years
2	25	Left undescended testis	Ipsilateral inferior RA muscle and sheath	Normal feel, symmetrical size	No defect abdominal wall
3	27	Right indirect inguino-scrotal hernia (congenital) Left undescended testis	Contralateral flap De-epidermised. Scrotal	Normal feel, symmetrical size	Large scrotum opposite side
4	31	Infected chronic haematocele (R)	Ipsilateral inferior RA-based dermofat pedicle	Normal feel, symmetrical size	Excision testis with coverings and tethered skin
5	25	Left undescended testis	Ipsilateral inferior RA MC de-epidermised flap	Normal feel, symmetrical size	MacGregor's flap raised but abandoned as damage to pedicle, late necrosis of returned flap
6	45	Left hydrocele Right undescended testis + hernia	Bipedicled contralateral flap De-epidermised Scrotal	Normal feel, symmetrical size	Flap shifted across septum
7	64	Carcinoma penis Left calcified haematocele 8 years	Partial amputation penis Contralateral and ipsilateral de-epidermised scrotal flap	Normal feel, symmetrical size	Penile stump lengthened, covered right anterolateral (long) and left anterolateral (short) scrotal flaps. Large scrotum

RA = rectus abdominis. MC = myocutaneous

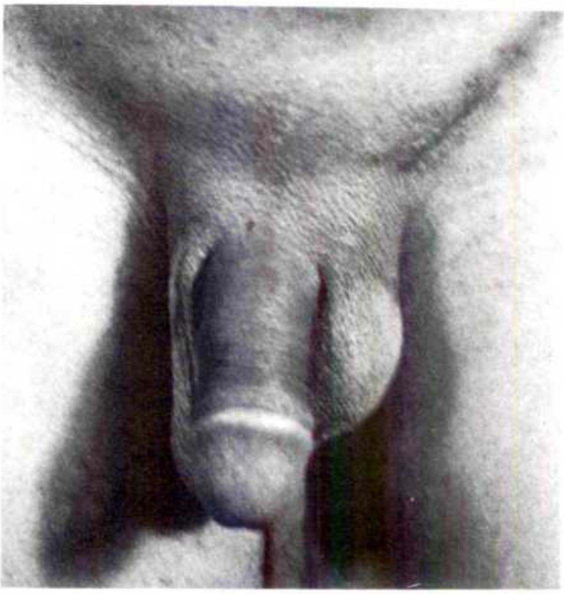

Fig. 1 Case 1. Two years after ipsilateral inferior partial rectus abdominis myocutaneous de-epidermised flap.

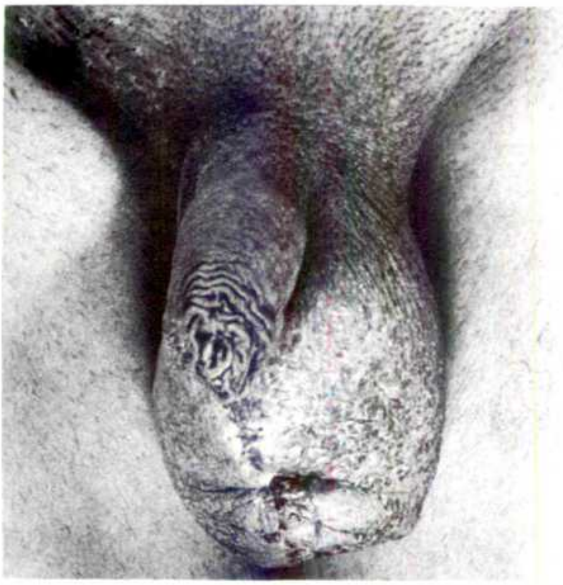

Fig. 2 Case 6. Large scrotum on left side due to hydrocele and undescended right testis. Result of scrotal bipedicled flap.

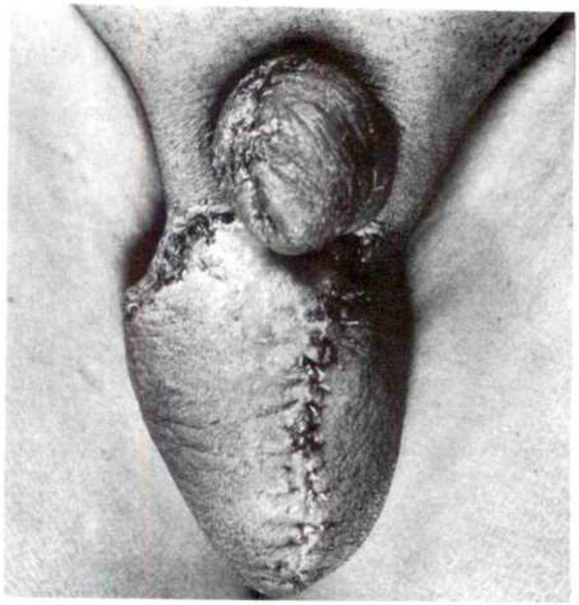

Fig. 3 Case 7. Result after double folded scrotal flap. The penis was lengthened and covered with an anterolateral scrotal flap.

posterior flap with partial anterolateral extension was used to fashion a testis (Fig. 3). In all cases the skin was de-epidermised and the pedicled end was incised to the level of the dartos in order to preserve the blood supply.

Vascularised autogenous tissue remains the most acceptable material. Rectus abdominis-based flaps have the disadvantage of an abdominal scar and possible abdominal weakness, though no problem was encountered in our four patients. Scrotal skin is preferable, if sufficient is available, because it has an excellent blood supply.

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Taylor, G. I., Corlett, R. and Boyd, J. B. (1983). The extended deep inferior epigastric flap: a clinical technique. *Plastic and Reconstructive Surgery*, **72**, 751-764.

Requests for reprints to: S. Parkash, Department of Surgery, Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry - 605006, India.

British Journal of Urology (1987), 59, 99-100

Correspondence

re Interstitial cystitis

Letter to the Editor. Our group has been interested in interstitial cystitis for many years and we would like to comment upon the article by F. Parivar and R. A. Bradbrook ("Interstitial cystitis." *Br. J. Urol.*, **58,** 239-244, 1986).

We completely agree that the mucous surface coat of the bladder with its content of glycosaminoglycans and its cytoprotective effects plays a key role in the pathogenesis of interstitial cystitis. However, newer electron microscope studies (Dixon *et. al.*, 1986) have shown that patients with interestitial cystitis have a mucin layer which is morphologically intact in normal controls. The biochemical composition of the layer may differ in patients with interstitial cystitis and this possibility is being investigated.

As mentioned by Parivar and Bradbrook, a controlled clinical trial comparing Elmiron with placebo has just ended. Unfortunately, it showed that Elmiron was not superior to placebo in the treatment of patients with painful bladder disease or interstitial cystitis (Holm-Bentzen *et al.*, 1986). Elmiron is a synthetic heparin-like drug and in theory it should be effective in the treatment of interstitial cystitis but only a small proportion is excreted in the urine and this may explain the lack of clinical effect. Clinical trials of subcutaneous heparin versus placebo have been initiated.

References

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Holm-Bentzen, M., Jakobsen, F., Nerstrøm, B., Lose, G., Kvist, Kristensen, J., Hald Pedersen, R., Krarup, T., Foggetter, J., Bates, P., Barnard, R., Larsen, S. and Hald, T. (1986) A prospective double-blind clinically controlled multicenter trial of Elmiron (sulphopentosan sodium) in the treatment of interstitial cystitis and related painful bladder diseases. *J. Urol* (In press).

M. Holm-Bentzen and T. Hald,
Department of Urology,
Herlev Hospital,
2730 Herlev,
Denmark.

Reply by R. A. Bradbrook. I was very interested to learn that recent electron microscope studies have shown patients with interstitial cystitis to have an intact mucin layer and agree that investigation of the biochemical composition of this layer is important. It was disappointing to learn of the failure of Elmiron in clinical trial, but I still consider that the mucin layer is probably the key to this disease.

R. A. Bradbrook,
Department of Urology,
Torby Hospital,
Lawes Bridge,
Torquay TQ2 7AA.

re The risk of tumour implantation following "Abercrombie" modified nephroureterectomy

Letter to the Editor. It is worrying that Messrs Hetherington *et al.* ("Modified nephroureterectomy: a risk of tumour implantation." J. W. Hetherington, R. Ewing and N. H. Philp. *Br. J. Urol.*, **58,** 368-370, 1986) found that of five patients who underwent nephroureterectomy with transurethral resection of the intramural ureter, two developed invasive recurrence at the site of ureteric resection. This has not been our experience.

Between January 1980 and December 1985 we have performed modified nephroureterectomy by a procedure similar to that described by Abercrombie in 19 patients. There was one post-operative death due to pulmonary embolus. The average age of patients was 69.2 years and the average length of follow-up is 23.5 months (range 7-65). Six of 18 patients had had previous superficial transitional cell carcinoma of the bladder; the remaining 12 had primary upper tract tumours.

One of the 18 patients had two Ta recurrent tumours at the site of the ureteric orifice resection and five patients have had new occurrences at other sites in the bladder. No patient has developed an invasive tumour in the bladder or pelvis.

The difference between the experience of two urological centres is difficult to explain. It is possible that operative technique may play a part. It has been our practice at the completion of the resection to coagulate the end of the remaining ureter very thoroughly with a ball electrode. This seals the ureter in the hope of preventing tumour cell dissemination and also helps to identify the resected margin, confirming that the whole ureter has been removed by the open part of the procedure. We use a continuous flow resectoscope to minimise extravasation during the resection, with glycine irrigant, and resect the intramural ureter widely with a 2-cm margin of normal mucosa to prevent local superficial recurrence. This also ensures free drainage of the perivesical space back into the bladder postoperatively. Bladder irrigation with normal saline is started at the end of the operation and maintained for 24 hours. Catheter drainage is maintained for 7 days. An anterior approach is used for the nephrectomy. The pelvis and paracolic gutter are washed out with sterile water before closing the abdomen and a pelvic drain is left *in situ*.

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British Journal of Urology (1987), 59, 101-102

Notices

British Association of Urological Surgeons

President: Professor G. D. Chisholm, ChM, FRCS, FRCSE

Annual Meeting: Edinburgh, 30 June-3 July 1987

All correspondence to: R. G. Notley, MS, FRCS, Honorary Secretary, British Association of Urological Surgeons at the Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN.

DANTEC Urology Prize

An annual prize (formerly known as the DISA Urology Prize) will be awarded by DANTEC for the best scientific paper contributing towards the understanding of urinary tract function which has been accepted by a medical journal for publication in the United Kingdom. Special consideration will be given to papers relevant to clinical human urology. The prize will consist of a travel voucher for £400 and a token presentation gift. The winner will be notified before the BAUS Annual Meeting and the prize will be presented at the meeting.

The competition is open only to graduates of British or Irish universities resident in the British Isles. Papers which have been published from 1 January to 31 December of the year preceding the award will be considered.

All entries, which must include a reprint of the paper in question, must be submitted by 1 April in the year of entry to: The Honorary Secretary, British Association of Utological Surgeons at the Royal College of Surgeons, 35-43 Lincoln's Inn Fields, London WC2A 3PN.

The Bard Award

The award, which will consist of the sum of £1500 and the Bard Silver Medal, will be given at the Annual Meeting of the Association to be held in Edinburgh in 1987. The award is given for the best essay submitted specifically for consideration for the award by members of the Association and a paper, based on the successful essay and not exceeding 30 minutes' duration, will be given at a specified time in the programme of the meeting. The presentation of the award will then be made by the President.

Essays for consideration for the award should not exceed 35,000 words and six typewritten copies are requested. They should be submitted not later than 1 March 1987 to: The Honorary Secretary, British Association of Urological Surgeons at the Royal College of Surgeons, 35-43 Lincoln's Inn Fields, London WC2A 3PN.

Shackman Travelling Fellowship 1988

Applications are invited from Medical Practitioners registered in the United Kingdom who are Senior Registrars in an accredited Training Programme in Urology or Consultant Urological Surgeons of no more than 5 years' duration. Applicants of equivalent University status will also be considered.

The Fellowships are intended to provide sufficient support to enable the holder to undertake a period of study, either in the United Kingdom or abroad, for a period of not less than 6 weeks.

The subject to be studied must be related either to Urology or to Renal Transplantation and may be either a laboratory or a clinical investigation.

The closing dates for applications is 1 September 1987.

Further particulars from and all correspondence to: Taylors, Solicitors, 119 High Street, Newmarket CB8 9AG.

Urological Society of Australasia. 40th Annual Scientific Meeting

Rotorua, New Zealand. 8-13 March 1987

Further particulars from: H. Watts, P.O. Box 56, Tauranga, New Zealand.

Belgian Society of Urology—52nd Congress

Brussels, Belgium. 13-14 June 1987

The topic will be "Male organic impotence".

Further information from: F. Wart, Department of Urology, Institut Médico-chirurgical A. Gailly, Boulevard Zoé Drion 1, B-6000 Charleroi, Belgium.

Canadian Urology Association Meeting

Banff, Canada. 21-25 June 1987

Further particulars from: J. B. Metcalfe, Urology, 421 Medical Arts Building, 11010 Jasper Avenue, Edmonton, Alberta, Canada T5K 0K9.

Tenth International Symposium of the Ludwig Boltzmann Research Institute for Infections and Tumours of the Urinary Tract

Vienna, Austria. 19-21 February 1987

The main topics will be:

Topical and systemic chemotherapy of transitional cell carcinoma. Endoscopic interventions on the upper urinary tract. Erectile impotence: diagnosis and treatment.

Further information from: Secretariat of the Tenth International Symposium, c/o Vienna Academy of Postgraduate Medical Education, Alser Strasse 4, A-1090 Vienna, Austria.

Urological Days of Necker 1987

Paris, France. 12-14 March 1987

The topics will be:

Sexual ambiguities
Lymphatic spread in urological cancer

Further information from: Professor J. Cukier, Clinique Urologique, Hôpital Necker, 149 Rue de Sèvres, 75015 Paris, France.

Ninth International Course of Urology

Barcelona, Spain. 20-24 April 1987

The topic will be "Recent Developments in Urology".

Further particulars from: Dr P. Carretero, Chair of Urology, C/ Casanova 143, 08036 Barcelona, Spain.

First Copenhagen Symposium on Uroradiology, Imaging and Interventional Techniques

Herlev, Denmark. 7-10 September 1987

The topics will include: Upper Urinary Tract Imaging and Intervention, Lower Urinary Tract Imaging and Urodynamics, Reflux Nephropathy, The Poorly Functioning Kidney, The Transplanted Kidney, Malignant Disease of the Kidney and the Urinary Tract, Renovascular Hypertension.

Further information from: H. S. Thomsen, Department of Diagnostic Radiology 54 E2, KAS Herlev, Ringvej, DK-2730 Herlev, Denmark.

World Congress of Surgery

Sydney, Australia. 20-25 September 1987

Urologists are invited to attend this meeting and contribute to the urological programme.

Abstract forms and further information from: B. Pearson, 100 Carillon Avenue, Newtown, NSW 2042, Australia.

International Study Group for Steroid Hormones: 13th Meeting

Rome, Italy. 30 November-2 December 1987

The topics will include:

The testis: basic and clinical aspects
Physiopathology of ovulation
Endocrine-related hypertension

Further particulars from: Professor F. Sciarra, V Clinica Medica, Università di Roma "La Sapienza", viale Policlinico, Rome 00161, Italy.

Journal Cover

The crest on the cover is a photograph of the BAUS Presidential badge.

The shield is taken to represent the bladder. The sun in the upper left-hand corner is the emblem of Apollo, the god of medicine. The ship symbolises the home and overseas nature of the Association. The golden sea represents the urine. The two dolphins at the foot of the shield mark the openings of the ureters in the bladder. The background above the shield is filled by two pyelograms, decoratively treated, whose ducts turn and descend behind the shield, to enter it at the openings marked by the two dolphins. Above, the crossed keys of heaven—the emblem of St Peter—commemorate the work of St Peter's Hospital. The scroll on either side bears the motto "Vis Unita Fortior"—a further allusion to the worldwide activity of the British Association of Urological Surgeons.

Quoted from John Everidge 1949

British Journal of Urology (1987), 59, 103–104

Book Reviews

Advances in Internal Medicine. Volume 31. Edited by G. H. Stollerman, W. J. Harrington, J. T. Lamont, J. J. Leonard and M. D. Siperstein. Pp. xxvii+551. Chicago, London: Year Book Medical Publishers. 1986. Price £53.50.

While it is improbable that urologists would invest £53.00 in a book of this title, they may be interested to learn where to find a number of first class, state-of-the-art contributions to many aspects of medical care. The subjects are wide-ranging and fascinating.

Key words such as T-cells, rejection, oncogenes, β-lactam antibiotics, computers, pulmonary embolism, sarcoid, stones in the common bile duct, cirrhotic ascites and diabetic vascular disease give some indication of the scope of the chapters where major advances are described. The final chapter "Management of a patient recovering from myocardial infarction. a decision tree" is an excellent summary of current thinking, treatment options and guidance that is characteristic of this book.

Surgery of Female Incontinence. Second edition. Edited by S. L. Stanton and E. A. Tanagho. Pp. xx+285. Berlin, Heidelberg, New York, Tokyo: Springer-Verlag. 1986. Price DM160,/(approx. £47.00).

A second edition of this already excellent book after 6 years has allowed the editors to expand their subject by over 40% with five new contributors and six new chapters. These changes have allowed many useful additions, notably chapters on congenital causes of incontinence, the abdomino-perineal urethral suspension (Zacharin) as well as two chapters on voiding dysfunction after bladder neck surgery. Useful improvements are noted in a number of chapters, especially the illustrations of the Stamey procedure. The final chapter offers a novel summary and a guide to the choice of surgery by the two editors. These additions and revisions now confirm the place of this book as the leader in this subject.

Infertility in the Male. (Current Reviews in Obstetrics and Gynaecology.) By Anne M. Jequier. Pp. 154. Edinburgh, London, Melbourne, New York: Churchill Livingstone. 1986. Price £18.00.

This small volume is aimed at the gynaecologist and gives a good but simple coverage of male infertility There is a need for all clinicians managing infertility to be well versed in both male and female problems and this book should help towards this need in British gynaecological practice.

Essentials of Urology. Edited by J. N. Corriere, Jr. Pp. xi+353. New York, Edinburgh, London, Melbourne: Churchill Livingstone. 1986. Price £29.00.

This soft cover book was written for medical students and residents by contributors all of whom are, or were, members of the University of Texas Medical School at Houston. It has therefore an almost entirely North American approach to the subject, to the references and to tumour staging. The text is clear, straightforward and uses many lists for signs, tests and protocols in urology. It achieves its aim of a comprehensive introduction to urology for students but residents would need much more information than is given in this basic text. It has not been competitively priced.

Genitourinary Oncology. Edited by D. A. Culp and S. A. Loening. Pp. xii+632. Philadelphia: Lea and Febiger. 1985. Price US $112.25.

There have been a number of texts on this topic in recent years and an even larger number of books devoted to a urological tumour or even some aspects of one tumour. The great attraction of this book is its style and balance in covering this subject. There are general chapters on cancer therapy that review the principles of management; then each specific tumour site is described in a systematic and very readable manner. This book is well referenced and the index is good. This book is highly recommended for a balanced view of urological tumours.

Rob and Smith's Operative Surgery. Urology. Fourth Edition. Edited by S. Scott McDougal. Pp. xxv+777. London: Butterworths. 1986. Price £98.00.

The Fourth Edition of this excellent urology volume in the Rob and Smith's Operative Surgery series has many changes and a number of new chapters. The increasingly international field of contributors reflects the impact of the editor, Professor Scott McDougal of Vanderbilt University. In the decade since the previous edition, urology has undergone many major changes both in emphasis and in methods of treatment, and the doubling in the size of this book takes account of much of this progress.

It is clearly a reference book where the reader will seek detailed descriptions, especially of newer and less commonly practised procedures. However, there is an imbalance between these and the commonplace, *e.g.* the allocation to drainage of the bladder is the same as that for cystoplasty. Also there is imbalance in the proportion of text to figures between the chapters, so that some are detailed while others are very skimpy. There is discussion on percutaneous techniques but not in much detail and the trainee seeking detail in things currently discussed, though not always practised, such as continent diversion, "clam" enterocystoplasty, Nesbit's procedure for Peyronie's disease, Stamey's procedure for incontinence and even ureteroscopy, will be disappointed.

The descriptions and drawings are, with few exceptions, excellent and despite its shortcomings this book is an invaluable reference source that should be in a departmental or hospital library.

Books Received

Recent Advances in the Treatment of Urinary Tract Infections. International Congress and Symposium Series Number 97. Edited by F. H. Schroder. Pp. ix + 59. Published by Royal Society of Medicine Services, London. Distributed by Oxford University Press. 1986. Price £7.50.

Role of the Sympathetic Nervous System in the Lower Urinary Tract. Edited by R. S. Kirby, E. J. Milroy and M. Mitchell. Pp. 1s–77s. *Clinical Science*, 70, Supplement No. 14. London: Medical Research Society and Biochemical Society. 1986.

Proteinuria and the Nephrotic Syndrome. Edited by D. E. Hricik and M. C. Smith. Pp. x + 198. Chicago, London: Year Book Medical Publishers. 1986. Price £31.50.

Tomodensitométrie du Rein et du Rétropéritoine. By G. Lemaître, A. N. Dardenne and C. Caron-Poitreau. Pp. viii + 119. Paris, New York, Barcelona, Milan, Mexico, Sao Paulo: Masson. 1986. Price 450 Fr. F.

Échographie de l'Appareil Urinaire. By D. Matter. Pp. xii + 163. Paris, New York, Barcelona, Milan, Mexico, Sao Paulo: Masson. 1986. Price 398 Fr. F.

Séminaires d'Uro-néphrologie. Volume 12. Edited by C. Chatelain and M. Legrain. Pp. viii + 195. Paris, New York, Barcelona, Milan, Mexico, Sao Paulo: Masson. 1986. Price 256 Fr. F.

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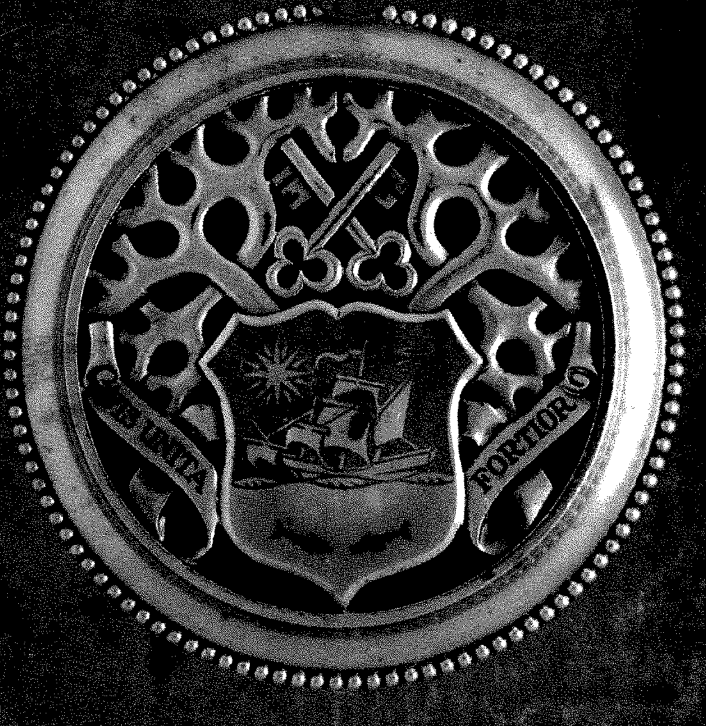

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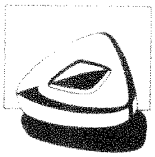

ferences: 1 Iacovou JW. Dunn M. Br J Urol 1987; 60: 526-8. **2** Gower R, Wells P. Neurourol Urodyn 1988; 7: 216-7. **3** Stott MA. Abrams P. Neurourol odyn 1988; 7: 217-8.

escribing Information. Presentation: 'Doralese tab' Tablets. PL 0002/0168, each containing mg indoramin. 60 (4 x 15). £8.40. **Indication:** anagement of urinary outflow obstruction due to nign prostatic hypertrophy, particularly in patients whom surgery is contra-indicated or delayed. **sage and administration:** *Adults only:* 20 mg b.d. rease if necessary in increments of 20 mg at veekly intervals to maximum of 100 mg a day in ided doses. *Elderly:* 20 mg at night may be equate. **Contra-indications:** Established cardiac ure; treatment with MAO inhibitor. **Precautions:** rowsiness occurs, avoid driving or operating machinery and CNS depressants including alcohol. Hepatic or renal insufficiency, Parkinson's disease, epilepsy, history of depression. Control incipient cardiac failure before treatment. Possible potentiation of hypotensive action of thiazide diuretics, beta-blockers or other antihypertensive drugs. Adjust dosage of latter if necessary. **Adverse reactions:** Initially drowsiness or sedation; also if dosage is increased too rapidly. Less commonly dry mouth, nasal congestion, weight gain, dizziness, retrograde ejaculation, depression. **Overdosage:** Possibility of deep sedation, coma, hypotension, convulsions, hypothermia. Suggested treatment includes gastric lavage, assisted ventilation, circulatory support and control of hypotension, intravenous diazepam for convulsions, slow rewarming for hypothermia. **Legal category:** POM. 9.12.88.

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References to books should be as follows:

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'ZOLADEX' PRESCRIBING NOTES. Use: Prostate cancer suitable for hormonal manipulation. **Presentation:** A sterile depot containing goserelin 3.6mg. **Dosage and administration:** One depot injected subcutaneously into the anterior abdominal wall every 28 days. **Precautions:** Care with patients at particular risk of developing ureteric obstruction or spinal cord compression. Consider initial use of an anti-androgen at the start of therapy. **Side effects:** Hot flushes, decrease in libido and occasional breast swelling and tenderness. Skin rashes (generally mild). Occasional mild bruising at injection site. Initial transient increase in serum testosterone may cause temporary increase in bone pain. **Product licence number:** 29/0198. **Basic NHS Price:** £114.00 per depot. 'Zoladex' is a trademark. Further information is available from: ICI Pharmaceuticals (UK), Southbank, Alderley Park, Macclesfield, Cheshire SK10 4TF.

Reference 1. Lunglmayr G, Girsch E. In Chisholm G D ed. *'Zoladex' – a new treatment for prostatic cancer. International Congress and Symposium Series.* 125. London: RSM Series, 1987: 47-51.

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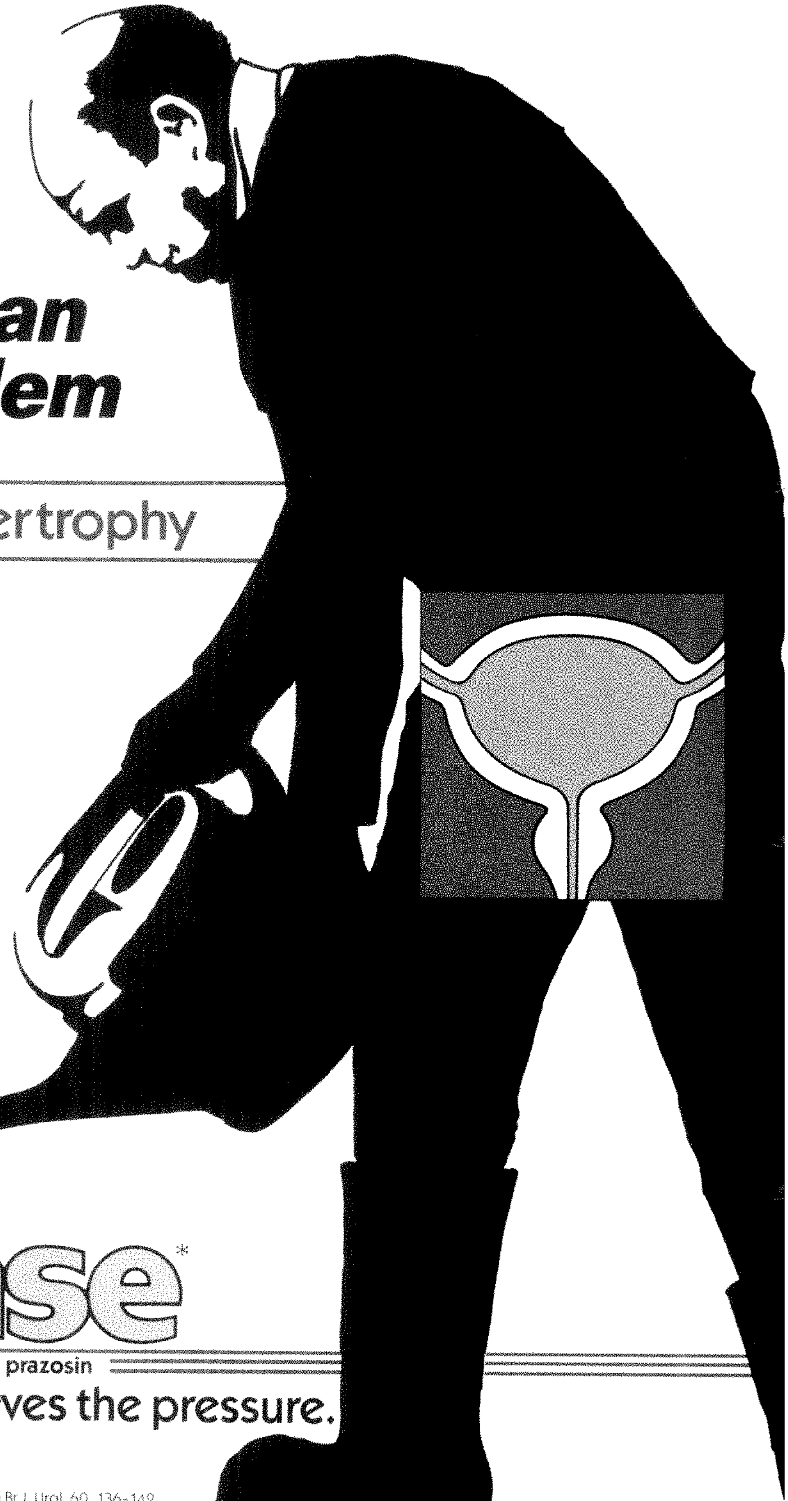

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Reference
1. Caine M. (1986) Clin. Sci. 70 (Suppl. 14) 63s-68s. 2. Kirby R.S. et al (1987) Br.J. Urol 60 136-142.

Prescribing Information in Benign Prostatic Hypertrophy

Indications: Hypovase* is indicated as an adjunct in the symptomatic treatment of urinary obstruction caused by benign prostatic hypertrophy. **Dosage:** The recommended starting dose is 500 micrograms twice daily for three to seven days, with the initial dose administered in the evening. According to the patient's clinical response, the dosage may be titrated upward to a maintenance dose of 2mg twice daily. This dose should not be exceeded, unless the patient requires Hypovase* as antihypertensive therapy. **Contra-indications:** Sensitivity to Hypovase.* **Warnings:** Hypovase* is not recommended for patients with a history of micturition syncope. **Precautions:** Hypovase* decreases peripheral vascular resistance and since many patients with this disorder are elderly, careful monitoring of blood pressure during initial administration and during adjustment of dosage is recommended. The possibility of postural hypotension, or rarely, loss of consciousness, as reported in other patient groups should be borne in mind. Hypovase* may augment the efficacy of antihypertensive therapy, consequently, close observation is especially recommended for patients taking medications that are known to lower blood pressure. **Side-Effects:** Dizziness is the most common. **Basic NHS Cost:** 500 microgram tablet (PL57/0270) pack of 100, £4.31; 1mg tablet (PL57/0271) pack of 100, £5.53; 2mg tablet (PL57/0272) pack of 100, £7.51, b.d. starter pack (8 × 500 microgram tablets plus 32 × 1mg tablets), £2.90. Further information on request.

*Trade Mark – prazosin hydrochloride

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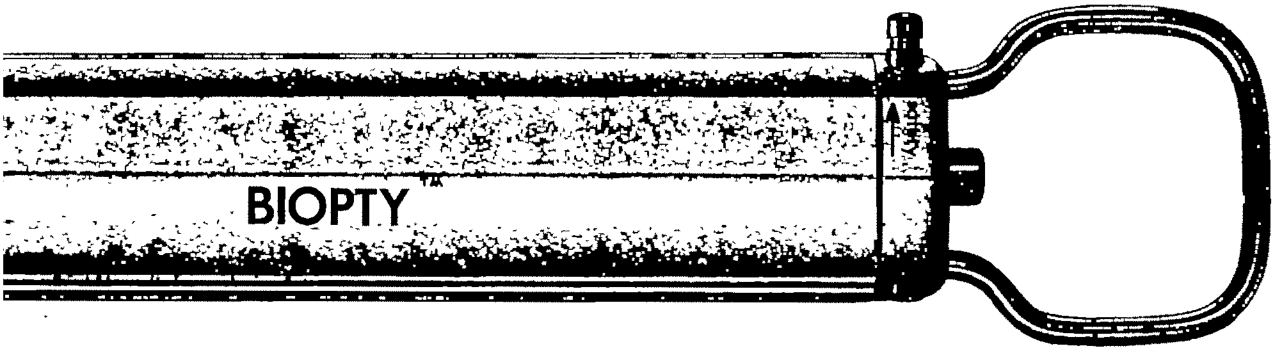

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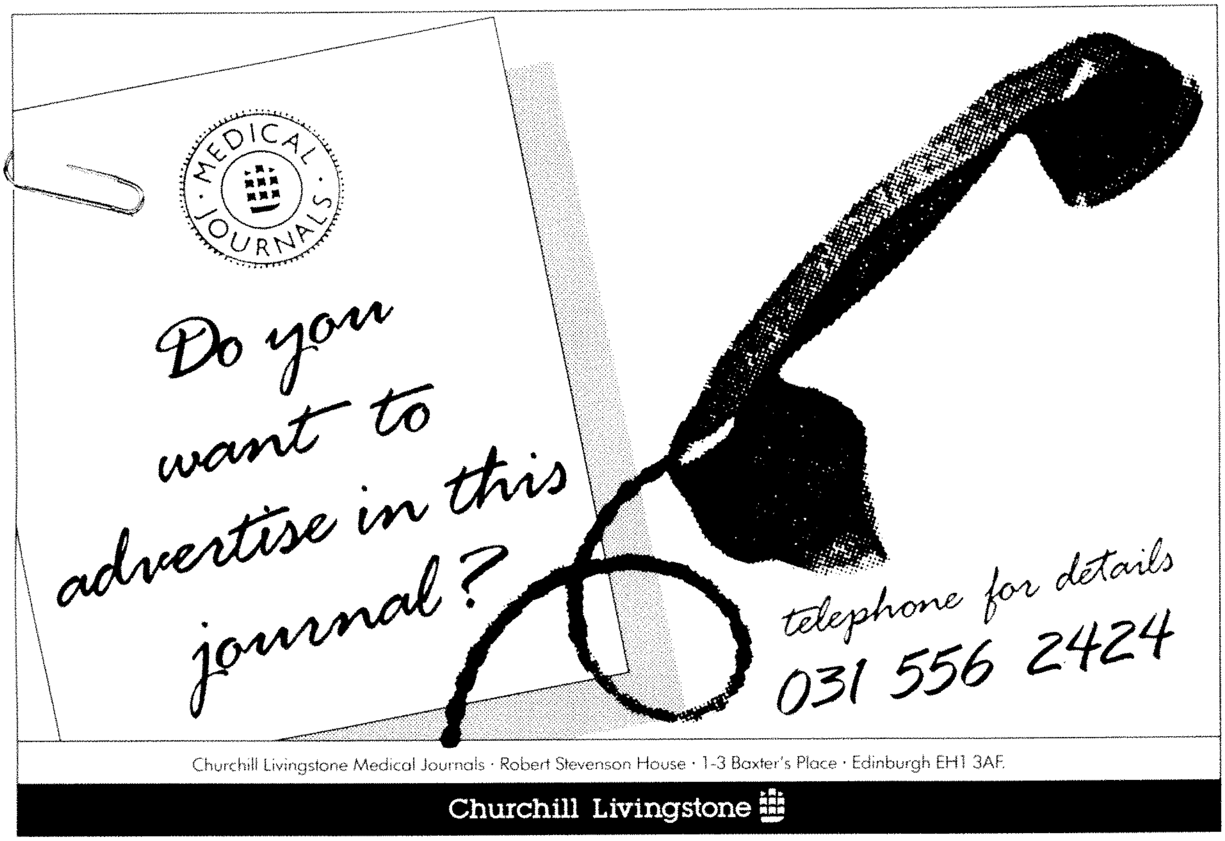

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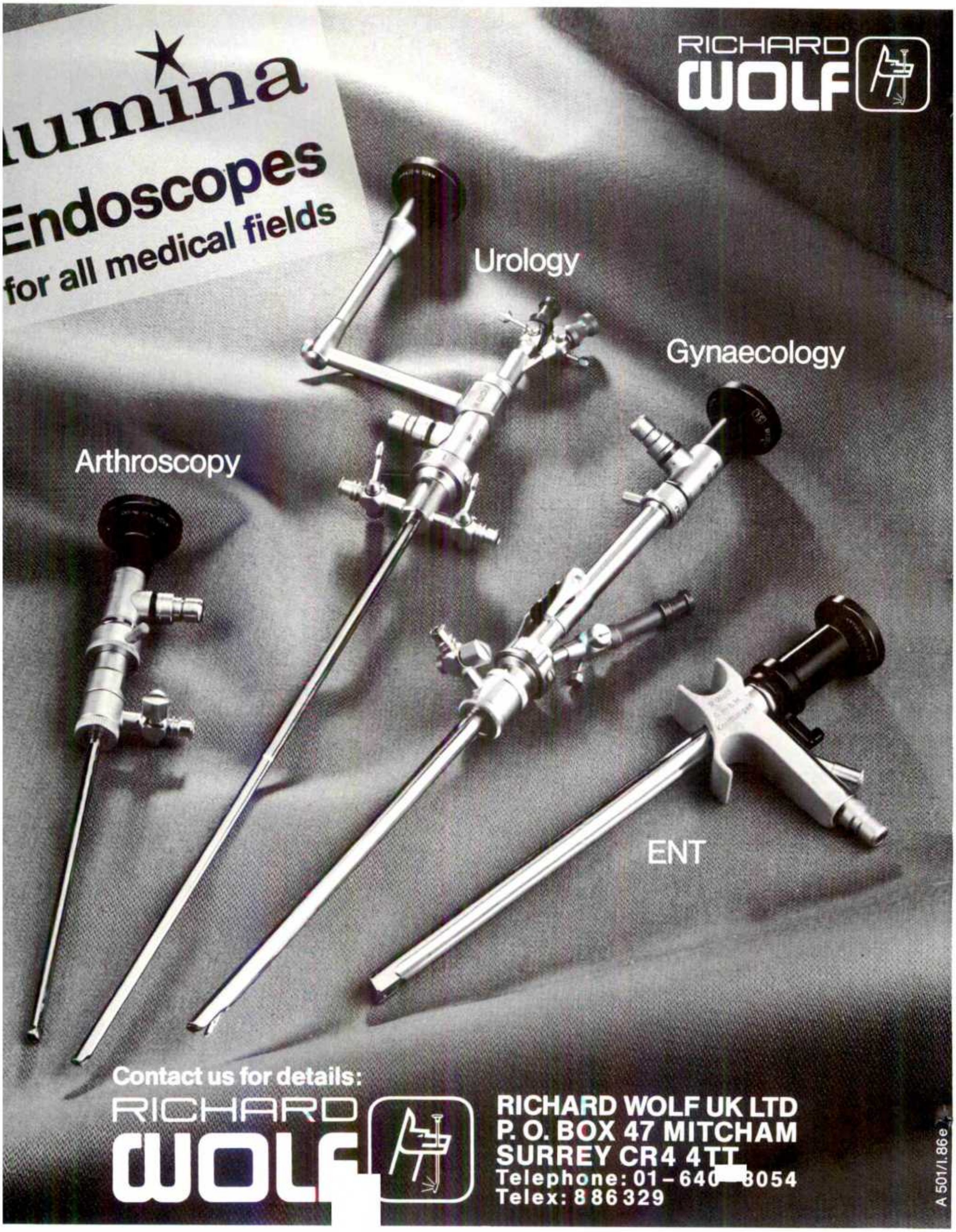

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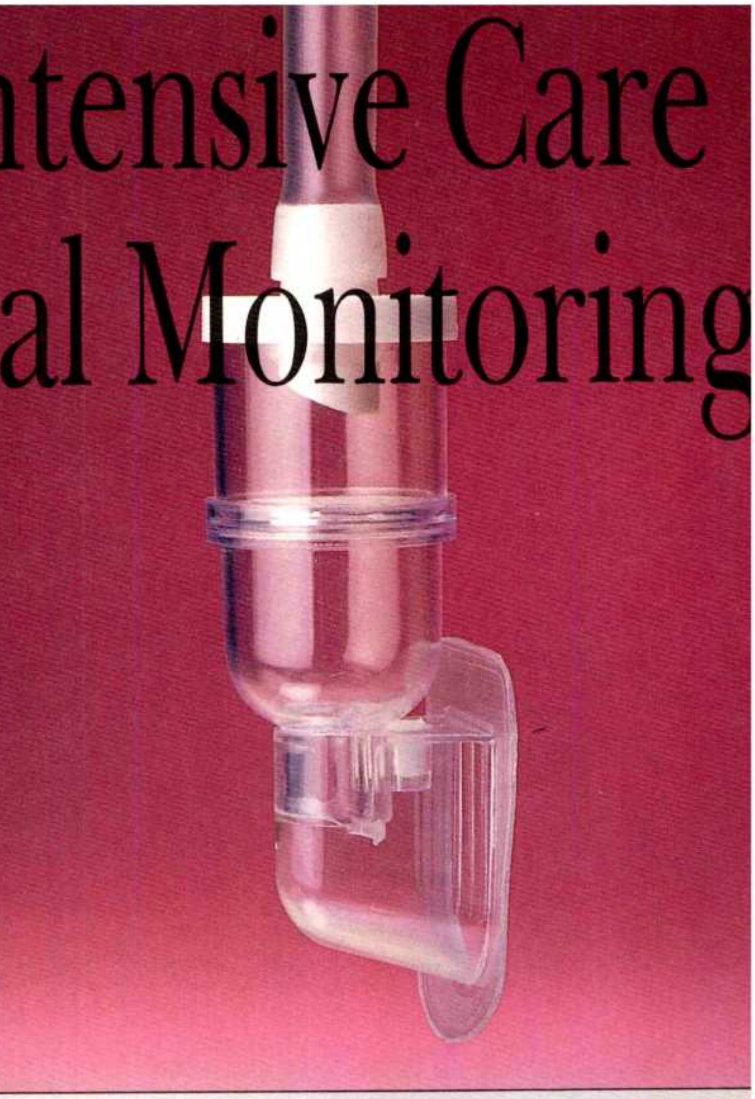

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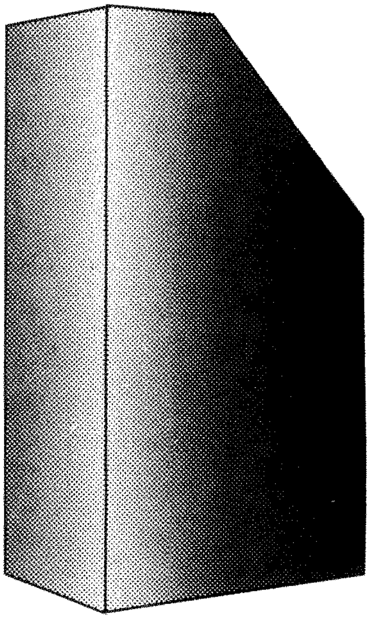

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British Journal of Urology (1989), 63, 337–339
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Presentation of Arms to the Urological Society of Australasia

D. URQUHART-HAY

Wellington, New Zealand

The Australasian Urological Society, founded on 7 January 1937, was granted the right to bear Arms in April 1987, coinciding with its Fiftieth Jubilee. During its Annual Scientific Meeting held in Sydney, 20–25 March 1988, at a ceremony held in the great dining hall of the University of Sydney in the presence of 200 members and their wives, Donald Urquhart-Hay presented to Harry Learoyd, President of the Society, Letters Patent from the College of Arms granting the Society the right to bear Arms.

The arms, comprising a shield, helmet, crest, supporters and motto, portray the origin, role and aspirations of the Society (Fig. 1). The shield, which is divided down the middle, bears the colours of Australia, green and gold, on the right side and on the left side the colours of New Zealand, black and silver. It is interesting that these 4 colours were those of the College of Barber Surgeons who received a grant to arms in 1569. In the centre of the shield is the badge of the Society. This represents the view seen through a cystoscope of the bladder neck with the lobes of the prostate suitably coloured in red with the urine portrayed in gold.

On top of the shield sits a steel helmet, visored and turned to the right. The mantling originally used to protect the head within the helmet from the heat of the sun is secured to the helmet by a wreath, in turn surmounted by the flowers of the yellow wattle of Australia and the red pohutukawa of New Zealand.

The crest is a lynx, an animal with exceptional vision. The ancients believed such keen vision could not have been provided by two eyes alone and they attributed this to some other unknown method of sight—hence the presence of supernumerary eyes scattered throughout its body as coloured circles or roundelles. It holds aloft in its forepaws an ancient instrument called an exploratorium used in the Marian operation for stone first described by Marianus Sanctus de Barletta in his second book "*Libellus aureus*" in 1543, a landmark in the history of urology. Around its neck it wears a crown with the 7-pointed stars of Australia and the 5-pointed stars of New Zealand.

On either side of the shield which they support are two early exponents of uroscopy, St Cosmos and St Damian. Twin brothers, Christian doctors, martyred under the Roman Emperor Diacletian (245–313 A.D.), they have been the patron saints

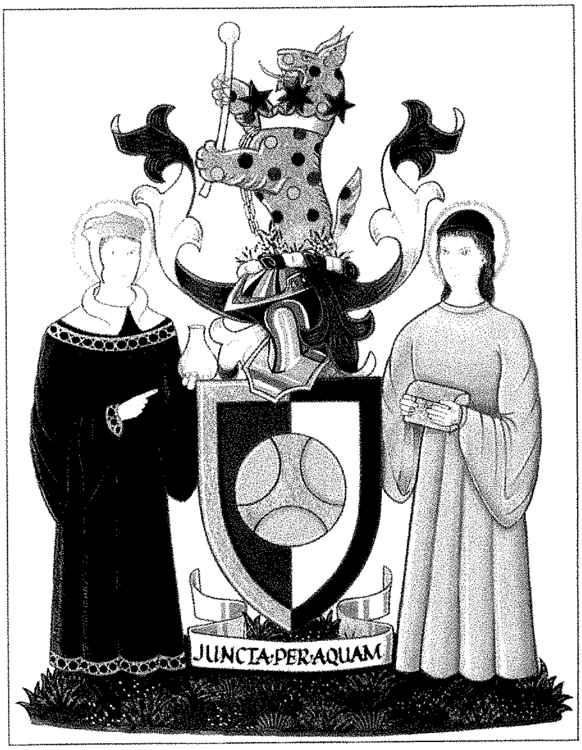

Fig. 1 Arms of the Urological Society of Australasia.

Accepted for publication 14 June 1988

of barbers and surgeons throughout Europe since the time of the Emperor Justinian (482–565 A.D.).

The motto—"*Juncta per aquam*"—joined across the water, emphasises in a humorous way the union of two countries separated by an ocean but working together within their "watery" medium.

The right to bear arms either individually or corporately is granted by the Sovereign. In practice, she delegates this responsibility to the Earl Marshal, who is the Duke of Norfolk. The College of Arms (of which he is the head) approves the design, records it and issues a document called Letters Patent which entitles either the individual or the corporate body the right to use those arms for ever. Those arms become the individual's or the society's personal property and anyone else displaying them is guilty of a civil wrong against which action can and has been taken.

The practice of heraldry is over 900 years old and its original intention was firstly to establish ownership, as in the use of seals, and secondly to establish identity, as in the field of war and tournaments. "Why", it may be asked, "should anyone need to design a coat of arms in the second half of the twentieth century?" Heather Child (1965) answered this by saying, "When arms became hereditary, the bearing of them signified continuity and a worthy pedigree so that a coat of arms has come to be a mark of historical identity and family continuity transcending the individual bearer. Is it then so surprising to find the modern usages of heraldry have their most popular developments in public activities? Coats of arms of corporate bodies such as banks, city councils, universities and the like are probably better known than those of any singular individual except the Arms of the sovereign—and the Royal Arms are a symbol of the monarchy itself. It is interesting that enterprises such as the Australian Broadcasting Corporation or the Atomic Energy Board without the least historical or military connection desire to obtain the stability of tradition and the mark of identity conferred by the possession of heraldic insignia. It is a touching thought that the new countries of Africa and Asia on ripening into political independence, found their national pride demanded not only a national anthem but elaborate coats of arms bearing, it is true, emblems that could be widely understood by their simpler peoples, but blazoned according to the ancient heraldic rules of a European tradition almost a thousand years old.

It is what heraldry stands for rather than the devices of which it is composed which gives public bodies the desire to own armorial bearings. It would be folly to claim that the practice, rules and grammar of heraldry are widely understood. However, they are widely accepted and the average citizen sees nothing comic in the highly-coloured coats of arms of his local authority or municipal dust-cart.'

The Letters Patent is a beautiful document some 24 × 18 in, made in vellum and painted by one of the highly skilled heraldic artists employed by the College of Arms (Fig. 2). In the top left hand corner is a picture of the arms of the Society, while at the top of the document are the arms of the Duke of Norfolk, the Earl Marshal, who issues the warrant, the Royal Arms with whom lies the power of grant, and the College of Arms who prepare and record the Letters Patent. The circumstances of the Society are recited and engrossed in the body of the document along with the blazon of the armorial ensigns. The document is signed by the three kings of arms, Garter, Clarencaux and Norroy and Ulster. Garter, who is Sir Colin Cole, is principal king of arms. Clarencaux, Sir Anthony Wagner, was previous Garter. He has written a number of standard works on heraldry, ancestry and the College of Arms itself and is, without doubt, the greatest authority on the English aspects of these subjects for very many years. Norroy and Ulster is Brooke-Little, another authority on heraldry who has written entensively on the subject. They have attached to the Patent their seals of office which depend from the document by means of blue corded silk ribbons and are contained in skippets or metal seal boxes.

Arms can be described in a sort of shorthand—a technical description in ancient Norman/French which to the experienced armorist works with the accuracy of a chemical formula. Although unintelligible to the uninformed, anyone with heraldic knowledge can understand a description precisely. Such a description is called a "blazon" and the blazon of the Society's arms is as follows:

Arms: per pale vert and argent a representation of the bladder neck seen through a cystoscope proper a border per pale or sable.

Crest: upon a helm with a wreath argent and sable issuing from a circlet composed of wattle and pohutukawa proper a demi lynx or roundelly of various tinctures grasping between its paws an exploratorium argent about its neck a circlet argent having as its finials four mullets two of five points one of seven manifest alternately sable from the circlet a chain argent.

Supporters: upon a grassy mound semee of wattle and pohutukawa on the dexter side a representation

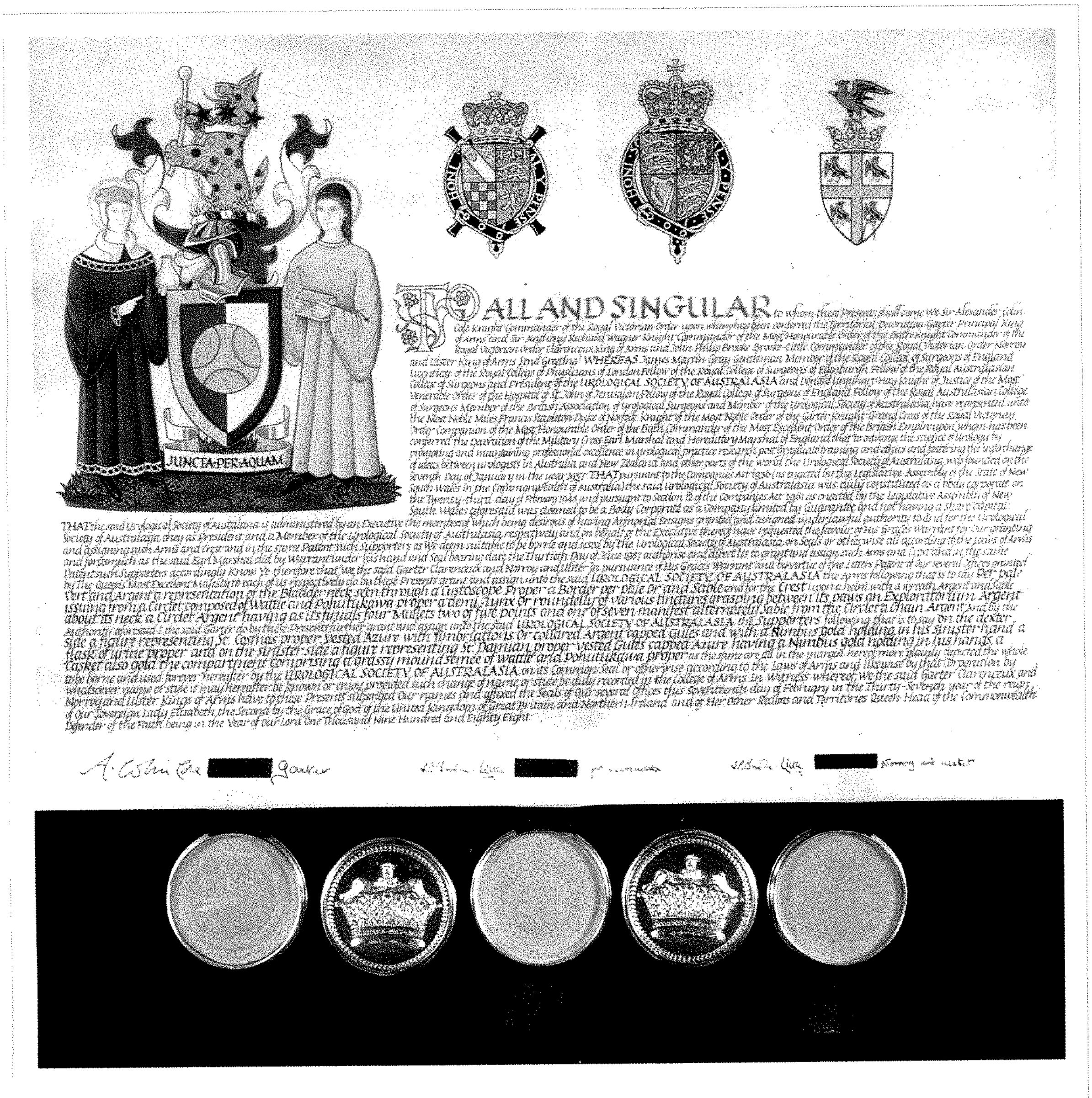
TO ALL AND SINGULAR
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Fig. 2 Letters Patent.

of St Cosmos proper vested azure with fimbriations or collared argent capped gules with a nimbus gold holding in his sinster hand a flask of urine proper and on the sinster a representation of St Damian proper vested gules capped azure with a nimbus gold holding in his hands a casket gold.

Motto: *juncta per aquam.*

The Society takes great pride in this royal recognition and honour.

Reference

Child, H. (1965). *Heraldic Design*. Pp. 19–22. London: Bell and Sons Ltd.

The Author

D. Urquhart-Hay, FRCS, FRACS, Consultant Urologist, Wellington Hospital, Wellington, New Zealand.

Requests for reprints to: D. Urquhart-Hay, Kelvin Chambers, 16 The Terrace, Wellington, New Zealand.

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Effect of Unilateral Vesicoureteric Reflux on Renal Growth and the Uptake of ^{99m}Tc DMSA by the Kidney. An Experimental Study in the Minipig

MARGARET L. GODLEY, R. A. RISDON and P. G. RANSLEY

Institute of Child Health, London

Summary—The influence of unilateral vesicoureteric reflux (VUR) on renal growth and the uptake of ^{99m}Tc DMSA by the kidney has been investigated in a 2-kidney model in the growing minipig over a period of approximately 5 months. Animals with reflux in association with low voiding pressures and normal bladder function ($n=5$), as well as those with raised voiding pressures and abnormal bladder function ($n=7$), were investigated with appropriate non-refluxing controls ($n=12$). Urinary infection and renal scarring were avoided since these factors may affect kidney function and growth independently.

Statistical tests of difference failed to demonstrate any effect of VUR on renal growth or renal uptake of ^{99m}Tc DMSA even in the presence of elevated voiding pressures and abnormal detrusor function.

In a recent experimental study using a 1-kidney pig model (Ransley *et al.*, 1987) we were unable to demonstrate any effect of vesicoureteric reflux on renal growth or function measured by glomerular filtration rate (GFR). VUR was, however, associated with a small decrease in urinary concentrating ability.

We now report an investigation which was carried out in parallel with and mostly employed litter mates of the animals used in the work cited above. For this study both kidneys were retained and VUR induced on one side only. The 2-kidney model allows the performance of one kidney to be compared with that of the other, so minimising any effects of variation between animals on the results. The model is suitable for examining the influence of VUR on the renal uptake of ^{99m}Tc dimercaptosuccinic acid (DMSA), using the contralateral kidney for purposes of comparison. It also provides information on the effects of unilateral VUR on renal growth in the presence of a non-refluxing contralateral system.

As in the first series, the effects of VUR in the presence of both normal bladder function and bladder outflow obstruction were considered and we sought to eliminate the complicating factors of urinary infection and renal scarring so that the influence of VUR alone could be evaluated.

Material and Methods

Experimental design

A series of 27 piglets were assigned to refluxing or non-refluxing groups (Fig. 1A) and followed for approximately 5 months. The investigation protocol is outlined in Figure 1B. The animals were weighed weekly and the first determinations of DMSA uptake (in both groups A and B) and bladder voiding pressures by cystometry (CMG: group B) were undertaken 4 weeks after the animals had achieved a weight of approximately 7.5 kg (study week 0). At the end of the study period (weeks 15–19) all animals had determinations of GFR, bladder voiding pressures, urinary concentrating ability and renal uptake of DMSA. The animals in group B had an additional CMG, generally at week 10. At the end of the study period all animals were killed, the urinary tracts removed and the kidneys weighed.

Accepted for publication 13 July 1988

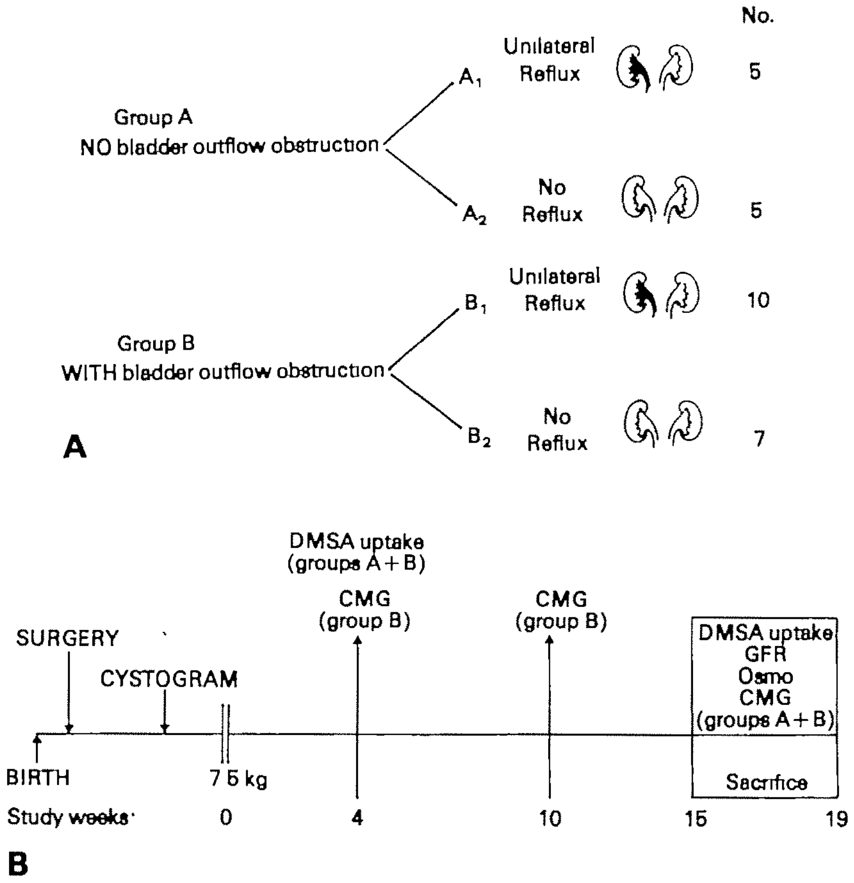

Fig. 1 (A) Experimental design. (B) Experimental protocol. Surgery. Group A—creation of VUR (A1), Group B—application of urethral ring (B1, B2), creation of VUR (B1). DMSA uptake: quantification of renal uptake of DMSA. CMG: cystometry. GFR ^{51}Cr EDTA glomeruler filtration rate Osmo: urinary concentrating ability

Experimental model

In weanling animals of group A1 and B1, left unilateral VUR was induced under halothane anaesthesia, by resecting the roof of the intravesical tunnel as described previously (Ransley and Risdon, 1978). In addition, animals in group B (both refluxing and non-refluxing) had a ring of silver wire (diameter 5–7 mm) placed around the urethra well below the bladder neck.

The animals had frequent ultrasound examination of the urinary tract for a week post-operatively and subsequently at the times of urine sampling (*vide infra*), using a Phillips SonoDiagnost R with linear array transducer.

Cystography to confirm the presence of VUR was performed as described previously (Ransley *et al.*, 1984) approximately 2 weeks after surgery in animals from groups A1 and B1.

Rectal temperatures were taken daily and urine samples were obtained by suprapubic puncture at approximately 2-weekly intervals for microbiological culture and microscopy of the centrifuged deposit. All animals received oral Macrodantin (50–200 mg/day) for the duration of the experiment, in addition to a single intravenous injection of gentamicin (2 mg/kg body weight) following surgery and manipulations involving suprapubic puncture.

Conscious filling and voiding cystometry, ^{51}Cr EDTA GFR and urinary concentrating ability were estimated as described previously (Ransley *et al.*, 1984, 1987) at the intervals detailed (Fig. 1B).

Renal growth

Renal growth was assessed by the weight of the kidneys at the end of the study and the relative weight calculated from the percentage ratio of the weight of the left kidney to the total renal weight (100*L/L+R).

Renal uptake of DMSA

DMSA (CisR) was radiolabelled using a pertechnetate generator (Amersham International plc) to provide a 5 ml solution containing 750MBq of activity. Precautions were taken to reduce pertechnetate contamination and to preserve the optimal DMSA-Tc complex as described previously (Godley *et al.*, 1985).

A weighed dose (approximately 25 μl/kg body weight) of DMSA was injected intravenously using a butterfly needle. At accurately timed intervals approximately 6 and 24 h later the renal activity was recorded (Nuclear Enterprises Mark V, high sensitivity collimation) for a pre-set time of 100 s in the posterior projection with the animal lying prone and in contact with the gamma camera face. The animals were lightly anaesthetised for each procedure. The dual area selection facility permitted 2 superimposed regions of interest of different sizes to be positioned over each kidney image to determine renal activity with background subtraction. The mean renal depth for each kidney was assessed ultrasonically and a correction made for attenuation of activity by tissue. The correction factor was derived from a graph obtained independently using a perspex phantom.

The renal uptake of DMSA was calculated as the percentage of the administered dose (uptake %/dose) as described previously (Godley *et al.*, 1985). The activity of the dose was calculated from the weight of the dose and the activity of a known weight of a standard drawn from the same preparation of DMSA and subtracting the activity of the residue in the dose syringe and butterfly. The activity of the standard, the residue and each kidney in turn was recorded from the same marked area of the gamma camera face.

The relative renal uptake of DMSA was calculated from the percentage ratio of the uptake by the left kidney to the total uptake by both kidneys (100* L/L+R).

At the end of the study period each renal uptake was a mean of 2 estimations separated by 1 week. The animals were usually killed following acquisition of the 24-h renal activity in the final uptake study. The activity of the isolated kidneys taken from 23 animals was recorded and the uptake calculated from these *ex situ* kidneys was compared with that obtained from the 24-h acquisition *in situ*.

Statistics

Regression analysis was applied to the log transformed ratio values and the interaction between bladder outflow obstruction and VUR was tested. If there was no interaction ($P > 0.1$), then separate estimates of the effects of bladder outflow obstruction and VUR were calculated, in each case taking the other variable into account.

The method of Altman and Bland (1983) was used to assess the agreement between the DMSA uptake calculated from the activity of the kidneys *in situ* and that calculated from the *ex situ* kidneys of the same animal.

Results

Experimental model

The data from 3 animals were excluded from the analysis because these animals did not conform with the otherwise homogeneous study group.

One of these animals developed incipient bladder decompensation (urodynamic category 7, *vide infra*) with a large residual urine volume. There was marked bladder wall hypertrophy, unilateral ureteric dilatation and the kidney showed some limited scarring.

In the second animal excluded, the left (refluxing) kidney was seen to be smaller than the contralateral kidney on the initial DMSA renal image at study week 4. Post mortem examination showed a dilated left ureter and fibrosis around the vesicoureteric junction; these appearances suggested that some early post-operative obstruction had occurred despite the fact that we had failed to detect this by ultrasound during this period.

The third animal was excluded because 2 positive urine cultures were obtained between study weeks 10 and 12. The relative kidney weight value for this animal was 3.7 standard deviations from the expected mean and thus appeared to be an outlier.

For the animals included in the experimental analysis no positive cultures were obtained from any of the urine samples and all kidneys were macroscopically normal, with no evidence of hydronephrosis. Bladder wall hypertrophy and minimal ureteric dilatation associated with VUR was present only in the animals from group B (with abnormal bladder function).

Renal function

At the end of the study the values for GFR/30 kg body weight and maximum urinary osmolality were similar for all 4 groups (A1, A2, B1, B2). These parameters were not the subject of primary investigation in this study but demonstrate the functional uniformity between the groups; the means and ranges of these values are shown in Table 1, together

Table 1 Age, Weight, Glomerular Filtration Rate and Urinary Concentrating Ability for Each Group at End of Study

	Normal bladder function				*Abnormal bladder function*			
	Group A1 *Unilateral reflux*		*Group A2* *No reflux*		*Group B1* *Unilateral reflux*		*Group B2* *No reflux*	
No. of animals	5		5		7		7	
	Mean	Range	Mean	Range	Mean	Range	Mean	Range
Age (weeks)	25.8	22–27	24.8	22–30	27.7	25–29	26.1	21–31
Weight (kg)	34.4	31–42	33.6	32–35	31.4	27–39	34.6	32–39
GFR (ml/min/30 kg body weight)	105	91–127	111	100–138	103	89–133	109	86–130
Osmolality (mosmol/kg)	1137	964–1258	1139	1000–1267	1125	934–1249	1094	938–1206

with those for age and body weight for each group of animals at the end of the study.

Urodynamic findings

As in the previous study (Ransley *et al.*, 1987), each urodynamic study was ranked (1–7) to provide an index of the functional disturbance to which the kidney was subjected in the presence of VUR.

The group A animals were observed to void normally throughout the study. Voiding cystometrograms at the end of the study showed a simple bladder contraction with a peak voiding pressure of up to 30 cm H_2O (median 25; females category 1, males category 2).

At the end of the study period the animals with a urethral ring (group B) all voided at higher detrusor pressures (50–75 cm H_2O, median 60) than the group A animals. Voiding was slow (up to 90s), incomplete and sometimes associated with a raised end filling pressure (category 3). In some animals unstable detrusor activity was observed with pronounced pre- and post-void contractions (category 4). The category for the 3 urodynamic studies in each animal of group B is shown in Figure 2.

Growth

The individual and relative kidney weights for each animal are shown in Table 2. There was no interaction between bladder function and reflux ($t_{20}=0.037$) and no significant effect of reflux on relative kidney weight ($t_{20}=0.77$).

Renal uptake of DMSA

The results of the differences between the *in situ* and *ex situ* estimates of DMSA renal uptake are shown in Table 3. There was good agreement for both the uptake %/dose and the relative uptake.

The uptake %/dose for individual kidneys and the relative uptake values for each animal at study week 4 and at the end of the study period are shown in Table 4. There was no interaction between reflux and bladder function either at week 4 ($t_{19}=0.88$) or at the end of study period ($t_{20}=0.62$) and no significant effect of reflux on relative uptake values either at study week 4 ($t_{19}=0.14$) or at the end of the study period ($t_{20}=0.13$).

Discussion

This experimental study employed a 2-kidney model in the growing pig in which unilateral VUR (consistently left-sided) was induced in the test groups. The effects of VUR were examined in animals with normal bladder function and low voiding pressures as well as in animals with abnormal bladder function induced by the application of a urethral ring and characterised by prolonged voiding at elevated detrusor pressures and sometimes by unstable contractions during bladder filling.

The urine was kept sterile and the size of the

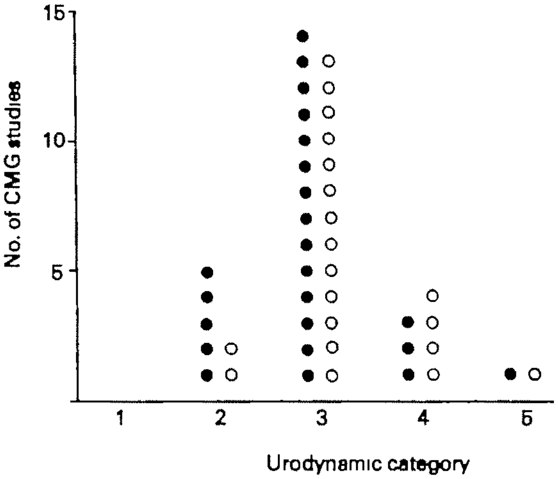

Fig. 2 Urodynamic categories (see text) for each of the urodynamic studies in animals of group B. (●: B1, ○: B2)

Table 2 Kidney Weights and Left Relative Kidney Weights (100* L/L + R) for each Animal

	Normal bladder function																
	Group A1 (Unilateral reflux)										*Group A2 (No reflux)*						
Pig. no.	—	—	*280*	*289*	*293*	*403*	*411*				*409*	*405*	*294*	*282*	*277*	—	—
Kidney weight (g)																	
Left	—	—	82	57	75	58	61	66.6 11.2	Mean SD	67.8 11.1	68	63	66	56	86	—	—
Right	—	—	82	55	73	52	61	64.6 12.6	Mean SD	64.4 12.1	69	57	61	52	83	—	—
Relative kidney weight %																	
Left	—	—	50.0	50.8	50.7	52.7	50.0	50.8 1.0	Mean SD	51.4 1.0	49.6	52.5	52.0	51.9	50.8	—	—
	Abnormal bladder function																
	Group B1 (Unilateral reflux)										*Group B2 (No reflux)*						
Pig. no.	*283*	*421*	*425*	*426*	*427*	*428*	*429*				*430*	*424*	*422*	*420*	*415*	*400*	*292*
Kidney weight (g)																	
Left	72	63	69	72	54	52	61	63.3 8.2	Mean SD	75.6 14.1	57	100	66	73	69	78	86
Right	71	59	68	71	56	51	64	62.9 7.8	Mean SD	73.1 12.0	57	91	66	74	65	74	86
Relative kidney weight %																	
Left	50.6	51.6	50.4	50.3	49.1	50.5	48.8	50.1 1.0	Mean SD	50.7 1.0	50.0	52.4	50.0	49.6	51.5	51.3	50.0

Table 3 Comparison between DMSA Uptake Calculated from the Kidneys within the Animal (*in situ*) with that Calculated from the Same Kidneys Isolated after *post mortem* (*ex situ*)

	In situ—ex situ difference		*Confidence limits 95% (+/−2SE)*
	Mean	*SD*	
Uptake %/dose			
Left	−0.64	1.46	−1.24 to +0.04
Right	+0.73	1.63	−0.02 to +1.44
Relative uptake %			
Left	−1.30	1.26	−1.85 to +0.75

urethral ring in the high pressure groups (B1 and B2) was tailored to provide stable bladder outflow obstruction without hydronephrosis. This was because we wished to avoid complicating factors such as infection, renal scarring and upper tract obstruction in examining the effects of VUR on the kidney. For these reasons, 3 animals (1 with upper tract obstruction, 1 with renal scarring and 1 with urinary tract infection) were excluded from the study. The present investigation complements a parallel one already published (Ransley *et al.*, 1987) which examined the effcts of sterile VUR in a 1-kidney model. The use of the 2-kidney model has allowed us to examine the effcts of VUR on renal growth in the presence of a non-refluxing contralateral system and to extend the functional studies to include the influence of VUR on the renal uptake of DMSA.

Renal growth

The effect of left unilateral VUR on the growth of the kidneys was assessed from consideration of the weight of the left kidney relative to the total renal weight, in comparison with non-refluxing control animals. The validity of using weight as an index of growth was discussed previously (Ransley *et al.*, 1987).

By the end of the experimental period the individual kidneys had achieved a weight of between 50 and 80 g. This implies that in the approximately 5-month period from the induction of reflux to the end of the study, the kidney weights had increased 4- to 5-fold when compared with the weights of the kidneys (mean 16.5 g) removed at unilateral nephrectomy in the parallel study from animals of the same age and body weight. Despite

Table 4 Uptake of DMSA by Individual Kidneys (uptake %/dose) and Left Relative Uptake (100*L/L+R) for each Animal at Week 4 and at End of Study Period

	Normal bladder function																
	Group A1 (Unilateral reflux)—pig no										Group A2 (No reflux)—pig no.						
	—	—	280	289	293	403	411				409	405	294	282	277	—	—
Uptake %/dose																	
Left	—	—	—*	21.3	17.8	25.0	23.9	22.0	Mean	20.7	18.7	23.3	21.3	19.9	20.3	—	—
								3.2	SD	1.7							
Week 4																	
Right	—	—	—*	22.8	17.2	24.1	19.4	20.9	Mean	20.5	22.0	20.5	22.1	19.9	18.1	—	—
								3.2	SD	1.7							
Left	—	—	18.8	17.8	20.1	21.2	21.2	19.8	Mean	20.8	19.5	23.0	19.8	20.2	21.4	—	—
								1.5	SD	1.4							
Weeks 15–19																	
Right	—	—	20.8	19.6	19.9	20.2	22.7	20.6	Mean	21.6	19.5	22.8	22.0	20.8	22.7	—	—
								1.2	SD	1.4							
Relative uptake %																	
Week 4																	
Left	—	—	—*	48.3	50.9	50.9	55.2	51.3	Mean	50.2	45.9	53.2	49.1	50.5	52.9	—	—
								1.1	SD	1.1							
Weeks 15–19																	
Left	—	—	47.5	46.9	49.9	48.7	48.1	49.0	Mean	49.1	50.4	47.9	45.6	47.4	47.6	—	—
								1.0	SD	1.0							

	Abnormal bladder function																
	Group B1 (unilateral reflux)—pig no										Group B2 (No reflux)—pig no						
	283	421	425	426	427	428	429				430	424	422	420	415	400	292
Uptake %/dose																	
Left	20.9	24.0	21.5	20.5	23.3	25.5	22.5	22.6	Mean	21.9	24.4	20.8	23.4	19.0	24.6	24.0	17.2
								1.8	SD	2.9							
Week 4																	
Right	21.3	24.0	22.0	20.2	26.8	23.2	24.9	23.2	Mean	22.1	24.3	20.5	24.9	19.2	24.7	23.3	17.5
								2.3	SD	3.0							
Left	21.4	18.9	26.1	23.5	20.1	27.3	24.4	23.1	Mean	21.3	25.5	22.7	21.7	17.7	20.5	22.3	18.7
								3.1	SD	2.6							
Weeks 15–19																	
Right	22.6	18.3	25.9	22.8	23.4	27.4	24.9	23.6	Mean	22.4	28.9	22.4	22.2	19.3	22.0	21.9	20.0
								2.9	SD	3.1							
Relative uptake %																	
Week 4																	
Left	49.5	50.0	49.4	50.4	46.5	52.4	47.5	49.4	Mean	49.9	50.1	50.4	48.4	49.7	49.9	50.7	49.6
								1.0	SD	1.0							
Weeks 15–19																	
Left	48.6	50.8	50.2	50.8	46.2	49.8	49.5	49.4	Mean	48.8	46.9	50.3	49.4	47.8	48.2	50.5	48.3
								1.0	SD	1.0							

* These values were not recorded because of technical problems

this rapid growth, the ratio of left to combined (left + right) renal weights was no different in animals with reflux than in non-refluxing controls even when reflux was occurring in the presence of abnormal bladder function and elevated detrusor pressures. Thus in this series of experiments, as in the parallel study employing the 1-kidney model, VUR had no influence on renal growth. Furthermore, these results corroborate the few clinical and animal investigations which consider the effects of VUR on renal growth in the absence of urinary tract infection and renal scarring (King and Sellards, 1971; Danforth *et al.*, 1980; Smellie *et al.*, 1981; Riebel *et al.*, 1982; De Gracia and Breuzière, 1984).

Renal uptake of DMSA

The uptake of DMSA by the left kidney relative to the total (left + right) renal uptake was calculated from separate estimations of the percentage of the administered dose taken up by each kidney (*i.e.* uptake %/dose). No effect of unilateral VUR on relative uptake was demonstrated even in the presence of abnormal bladder function and elevated detrusor pressures.

Care was taken to minimise errors associated with the preparation of DMSA, low renal counts, background activity and (most significantly) attenuation of activity by tissue depth. This last factor is of crucial importance even when estimating relative renal function. It cannot be assumed that the 2 kidneys are equidistant from the skin surface and an error of 1 cm in depth is equivalent to 13% error in renal activity (Gruenewald *et al.*, 1985; van Poppel *et al.*, 1985). In order to evaluate these errors the uptake values calculated from the kidneys *in situ* at 24 h were compared with those of the same kidney immediately after removal from the animal. Although the *in situ* and *ex situ* values were not indentical, the mean of the difference (*in situ*—*ex situ*) between the two was less than 1% (uptake %/dose) for both the right and left kidneys and the variation in these differences was small, indicating a good agreement between the two values. The results show that DMSA uptake by the left kidney was slightly underestimated whilst that of the right was slightly overestimated, producing a small negative bias in the left relative uptake.

There have been very few studies of the influence of VUR on renal uptake of DMSA. In a study measuring the absolute uptake as a functional index, Goldraich *et al.* (1984) found that renal uptake was normal in children with low grade VUR but was significantly lower than normal in those with high grade VUR; however, diminished uptake was never found in the absence of scarring and indeed a normal uptake was frequently observed in scarred kidneys. These results support those of our investigation, but whilst we can state that under the conditions of our experiment VUR *per se* has no effect on the renal uptake of DMSA, there are difficulties in interpreting these findings in the context of renal function. Despite the clinical use of DMSA in this respect, the precise mechanisms of its localisation in the cortical tubular cells are obscure, although a recent theoretical analysis suggests that DMSA uptake occurs predominantly by glomerular filtration and tubular reabsorption (Peters *et al.*, 1988). A number of clinical and experimental studies indicate that renal uptake of DMSA reflects various interrelated parameters. These include functional cortical mass (Kawamura *et al.*, 1979), renal blood flow (Daly *et al.*, 1979), effective renal plasma flow (Holten and Storm, 1979; Taylor, 1980; Daly and Henry, 1981), ^{99m}Tc DTPA glomerular filtration rate (Bingham and Maisey, 1978; Taylor *et al.*, 1986), creatinine clearance (Powers *et al.*, 1981; Baillet *et al.*, 1986) and tubular function (van Luijk *et al.*, 1983, 1984; Provoost and Aken, 1985). It follows that renal uptake of DMSA reflects the amalgamation of various parameters which together determine overall renal performance.

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Effect of Animal and Vegetable Protein Intake on Oxalate Excretion in Idiopathic Calcium Stone Disease

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Summary—Oxalate excretion was measured in healthy subjects and idiopathic calcium stone-formers on dietary regimens which differed in the type and amount of protein allowed; 24-h urine collections were obtained from 41 practising vegetarians and 40 normal persons on a free, mixed, "mediterranean" diet. Twenty idiopathic calcium stone-formers were also studied while on two low calcium, low oxalate diets which differed in that animal protein was high in one and restricted in the other.

Vegetarians had higher urinary oxalate levels than controls and although the calcium levels were markedly lower, urinary saturation with calcium/oxalate was significantly higher. This mild hypercalciuria was interpreted as being secondary to both a higher intake and increased fractional intestinal absorption of oxalate.

Changing calcium stone-formers from a high to a low animal protein intake produced a significant decrease in calcium excretion but there was no variation in urinary oxalate. As a result, the decrease in calcium oxalate saturation was only marginal and not significant.

It was concluded that dietary animal protein has a minimal effect on oxalate excretion. Mild hyperoxaluria of idiopathic calcium stone disease is likely to be intestinal in origin. Calcium stone-formers should be advised to avoid an excess of animal protein but the risks of a vegetable-rich diet should also be borne in mind.

The dietary manipulation of proteins has been found to induce changes in urinary biochemistry, but agreement has so far not been reached as to the effects on oxalate excretion in man. Robertson *et al.* (1979a) have shown that the consumption of large amounts of animal protein can markedly increase oxaluria and, conversely, that low animal protein intake can significantly decrease it (Robertson *et al.*, 1979b). Others have reported that dietary variation in animal protein has no effect on urinary oxalate (Butz *et al.*, 1980; Brockis *et al.*, 1982). Thus, Robertson *et al.* (1979a, b) advised stone-formers to become vegetarians, but others warned about the hazards of excessive amounts of vegetables in the diet.

We have studied urinary oxalate excretion in relation to variations in the amount and type of ingested protein.

Patients and Methods

The study was performed in two parts. In the first part, 81 subjects with no history of renal calculus or other renal disease were studied. Renal function, assessed by creatinine clearance, was normal in all subjects. Of these, 41 were vegetarians (22 males and 19 females; mean age 35.2 ± 12.1 SD years). The protein content of the diet in these subjects, derived from a retrospective enquiry, was approximately 59 g/day (range 40–80) (≈ 1.1 g/kg bw/day).

While milk and diary products were eaten regularly by 15 subjects, all abstained from eating flesh protein. All of the vegetarians consumed wholemeal or unprocessed bread, rice and pasta. They weighed slightly (but significantly) less than normal subjects (57.6 ± 9.5 *vs* 65.3 ± 10.2 kg; $P<0.01$).

The control group comprised 40 subjects (20 males and 20 females, mean age 36.9 ± 12.1 years) eating a free mixed "mediterranean" diet. The

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whole protein content of the diet was about 70 g/day (1.1 g/kg bw/day); animal protein represented 50 to 55% of the total protein intake.

The second part of the study was performed in 20 idiopathic calcium stone-formers (7 males and 13 females, mean age 39.8 ± 9.6 years) on two diets. In the first observation period animal protein intake was high (63 g/day or 0.95 g/kg bw/day) and restricted in the second (40 g/day; 0.6 g/kg bw/day). Mainly as a consequence of the above changes, the mean content of total protein was 95 g/day in the first diet and 70 g/day in the second. Calcium and oxalate supplies were kept low (10 mmol and 1.1 mmol/day respectively) during both diets and this was achieved by excluding milk and dairy products as well as spinach, rhubarb, cocoa, nuts and other oxalate-rich foods. Each of the above diets lasted for 1 month on average and the biochemical studies were performed a few days before the diet was withdrawn (usually on day 20). A wash-out period of about 15 days was allowed between the two diets.

Samples from 24-h urine collections on an outpatient basis were analysed by routine methods as described elsewhere (Marangella *et al.*, 1985). Oxalate determinations were performed by high performance ion chromatography (Mahle and Menon, 1982) using a Dionex-QIC apparatus. Since significant interference by ascorbate has been reported with this method, urinary ascorbate was routinely determined in samples from all of the normal subjects by means of the ascorbate-oxidase enzymatic method (Harris and Ajose, 1973), samples with an ascorbate concentration higher than 0.5 mmol/l were not run for oxalate and the subject was invited to repeat his urine collection. Total nitrogen excretion was estimated by the sum of urea, creatinine, uric acid and ammonia and considered as an index of the overall protein consumption. Urate and sulphate were assumed as raw indices of the dietary content in animal protein. Urinary saturation with respect to calcium oxalate monohydrate was calculated by our own computer technique (Marangella *et al.*, 1985) and expressed on a scale where values of 1 indicated saturation and more than 1 supersaturation. The results are listed as means ±(SEM) and the significance of differences assessed by the paired or unpaired Wilcoxon's test.

Results

The data from the two groups of healthy subjects are listed in Table 1. Significant differences emerged between vegetarians and controls; total nitrogen excretion was decreased in vegetarians owing to a decrease in the overall intake of proteins and, perhaps, in intestinal absorption of proteins from vegetables. Sulphate and urate were also decreased, as expected, by the low consumption of flesh protein. Calcium excretion was decreased and oxalate increased in vegetarians and there was a significant increase in calcium oxalate saturation in the urine samples from vegetarians.

The biochemical data obtained from the calcium stone-formers during the two study periods are shown in Table 2. The total nitrogen, sulphate and urate excretion was significantly reduced in patients on a restricted animal protein diet, indicating good patient compliance.

The protein-restricted diet produced a significant decrease in calcium excretion but failed to change urinary oxalate excretion or calcium oxalate saturation. Both of these parameters decreased slightly but not significantly.

Discussion

The influence of protein consumption on the biochemical profile of the urine in stone-formers is

Table 1 Comparison of Biochemical and Physicochemical Parameters in Urine from Vegetarians and Normal Controls on a Free Mixed Diet

Parameter	*Vegetarians (41)*	*Controls (40)*	*P*
Total nitrogen	580 (21.6)	711 (50.0)	<0.05
Urate	2.3 (0.09)	2.7 (0.14)	<0.05
Sulphate	16.5 (0.7)	19.2 (1.0)	<0.05
Calcium	2.8 (0.28)	4.3 (0.31)	<0.001
Oxalate	0.45 (0.02)	0.31 (0.02)	<0.001
Beta CaOx	7.8 (0.42)	5.7 (0.76)	<0.05

Biochemical parameters are expressed in mmol/24h Beta CaOx denotes urine saturation with calcium oxalate monohydrate, expressed on a scale where a value of 1 = saturation and more than 1 = supersaturation

Table 2 Comparison of Biochemical and Physicochemical Parameters in Urine from 20 Idiopathic Calcium Stone-formers on 2 Low Calcium, Low Oxalate Diets Differing in Animal Protein Intake

Parameter	*Low Ca-Ox/high animal protein*	*Low Ca-Ox/low animal protein*	*P*
Total nitrogen	979 (64.0)	712 (50.0)	< 0.001
Urate	4.2 (0.21)	3.15 (0.18)	< 0.001
Sulphate	27.1 (1.6)	19.1 (1.3)	< 0.001
Calcium	9.2 (0.40)	5.8 (0.36)	< 0.001
Oxalate	0.46 (0.04)	0.41 (0.04)	n.s.
Beta CaOx	10.6 (1.2)	8.3 (1.3)	n.s.

well recognised. There have been few reports on the effect of protein intake on urinary oxalate excretion and the results have been conflicting. Excess consumption of animal protein has been shown to cause a sharp increase in oxalate excretion (Robertson *et al.*, 1979a and b), which has been ascribed to the high content of amino acids such as tyrosine, phenylalanine and tryptophan (Gambardella and Richardson, 1977). By contrast, diets low in animal protein, as for example in vegetarians, are associated with low levels of urinary oxalate (Robertson *et al.*, 1979 a and b), although some studies have not been able to confirm this (Butz *et al.*, 1980; Brockis *et al.*, 1982; Pak *et al.*, 1984).

The results of the first part of the study showed that a vegetarian diet results in mild hyperoxaluria, despite a low intake of animal protein. There are reports that the Dionex technique for oxalate determination is liable to interference by ascorbate (Robertson and Scurr, 1984) and, indeed, high levels of urinary ascorbate in vegetarians could have affected our results. However, the routine measurement of ascorbate in urine from all of the healthy subjects and the rejection of samples with ascorbate concentrations above 0.5 mmol/l eliminated this problem. In addition, urinary ascorbate from our vegetarians was only mildly and not significantly higher than that from controls (90.8 ± 110 *vs* 52.6 ± 73.0 µmol/24h). Therefore our data conflicts with a previous study (Robertson *et al.*, 1979b) in which oxaluria in vegetarians was described as being in the lower limit of the normal range. These differences could reflect differences in the dietary habits or in sample composition of the two series. The mild hyperoxaluria found might be secondary to a high content of oxalate in vegetables usually eaten by the vegetarians in this country. We speculate, however, that the major cause of hyperoxaluria should have been intestinal hyperabsorption of oxalate secondary to both low intake and/or high binding of calcium in the intestinal lumen. The above mechanism might be enhanced by the high content of unprocessed bran in the diet, as suggested in previous reports (Shah *et al.*, 1980; Rao *et al.*, 1985). This is more likely to have occurred in our vegetarians, whose diet was richer in fibre than the diet of normal controls.

This hypothesis is also supported by the finding of urinary calcium levels inappropriately low with respect to calcium intake and by the finding of a weak but significant inverse correlation between calcium and oxalate in urine from vegetarians ($r = 0.355$, $P < 0.025$). The final result of the changes described is that the beneficial effects of a marked reduction in calcium excretion is overcome by the increase in oxalate excretion, so that urine on a vegetarian diet is more supersaturated with calcium oxalate than on a free mixed diet.

The second part of this study was designed to see whether changes in animal protein intake would result in significant changes in urinary oxalate. Reducing animal protein by approximately 30% in hypercalciuric stone patients on a low calcium, low oxalate diet had no effect on urinary oxalate and although there was a marked decrease in urinary calcium excretion, the decrease in calcium oxalate saturation was only marginal. It is possible that our failure to demonstrate any difference was due to the dietary manipulation being insufficient to influence urinary oxalate excretion. Indeed, Robertson *et al.* (1979a and b) were able to induce significant changes in urinary oxalate excretion by varying animal protein consumption by some 100% in normal volunteers. Our results demonstrate that fairly substantial restrictions (≈30%) in animal protein, as in our protein-restricted diets, failed to produce a significant reduction in urinary oxalate excretion. A mild hyperoxaluria, as is known to occur in idiopathic hypercalciuric stone-formers, due to intestinal hyperabsorption of oxalate, could account for these findings (Hodgkinson, 1978; Marangella *et al.*, 1984).

In conclusion, the restricted consumption of animal protein can produce a limited effect on animal protein can produce a limited effect on urinary oxalate if mild hyperoxaluria is likely to be absorptive in origin. However, the results of the present study do not allow us to exclude the possibility that excessive consumption of animal protein could induce high urinary oxalate, and calcium stone-formers should be advised to avoid this. These data also suggest that vegetable-rich diets may increase the intestinal absorption and urinary excretion of oxalate and stone-formers should also be cautioned about these counter-productive effects.

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Assessment of the Safety of Regular DDAVP Therapy in Primary Nocturnal Enuresis

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Summary—A group of 7 patients with refractory primary nocturnal enuresis on long-term DDAVP therapy (mean 13 months) were submitted to a standard water deprivation test in conjunction with a hormone profile and routine haematological and biochemical investigations. No abnormalities were demonstrated, which suggests that the drug is safe in this clinical situation.

The effective management of refractory nocturnal enuresis in both adults and children remains a challenge to clinicians. The arrival of the synthetic ADH peptide analogue DDAVP (l-desaminocysteine 8-D-arginine vasopressin) has been a significant advance in the symptomatic relief of the condition. When given in doses of 0.1 to 0.2 mg by intranasal spray at bedtime (Dimson, 1977; Tuvemo, 1978; Terho and Kekomaki, 1984), DDAVP effectively suppresses urine production for 7 to 10 h but lacks the pressor side effects of ADH (Ramsden *et al.*, 1982; Product Information, Ferring Pharmaceuticals Ltd). Its safety has been established in patients requiring long term therapy with the less common condition of diabetes insipidus. Prolonged use of DDAVP may be desirable in the management of patients with nocturnal enuresis when other agents fail, but concern has been expressed about its safety in this situation. This study was undertaken to asses this with particular emphasis on endogenous ADH secretion.

Patients and Methods

Four females and 3 males aged between 10 and 26 years (mean 17.7) with refractory primary nocturnal enuresis were treated with DDAVP for between 4 and 24 months (mean 13). All were otherwise in good health and received regular DDAVP with only infrequent omissions on which they usually remained dry at night; 5 patients were treated with DDAVP 0.2 ml *nocte* but in 2 patients 0.1 ml *nocte* was found to be sufficient to maintain nocturnal continence. Patient compliance could not be measured directly but all patients assured us that they had used DDAVP on a continual basis. In the younger patients therapy was under parental supervision. Each patient was admitted for a standardised water deprivation test (Mitchell *et al.*, 1972). DDAVP was omitted on the day of the test. Following a mid-day meal and 1 litre of fluid the patient received nil by mouth and was weighed. A urine specimen was taken at 1300 h. At 0700, 0800 and 0900 h the following day further urine samples were taken. The patient was weighed again before the fast was broken at 0900 h. Plasma cortisol was measured at 2345 and 0800 h. Blood samples were taken at 0800 h during the test for a biochemical and haematological profile.

Results

Our protocol requires that the urine osmolality exceeds 800 mosm/kg during a standard water deprivation test (Fig.). A measured weight loss exceeding 1.25 kg in each patient provided corroborative evidence of compliance.

A full blood count, blood urea, electrolytes and creatinine, liver function tests and a static endocrine profile of thyroxine, luteinising hormone, follicle stimulating hormone and prolactin were normal in all patients. The cortisol estimations showed a normal diurnal variation in each case. No variation

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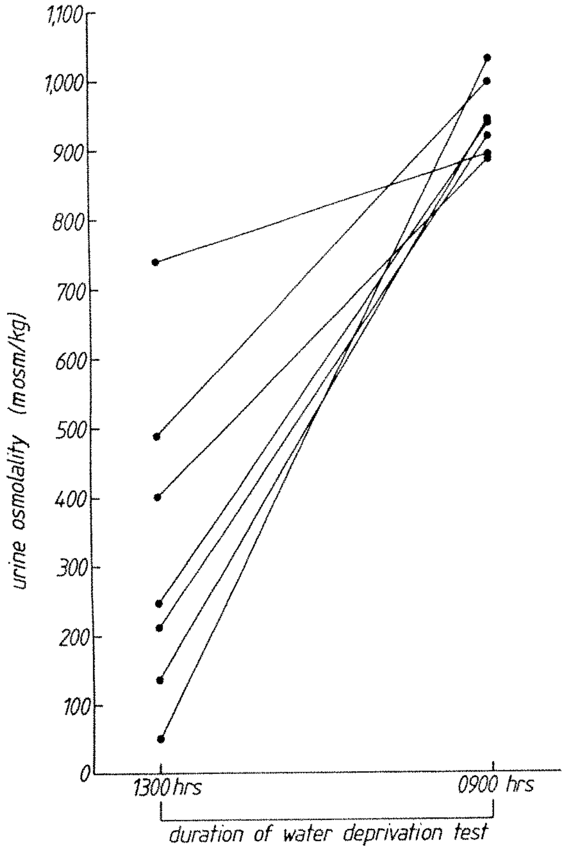

Fig. Results of water deprivation test in 7 patients receiving DDAVP therapy for nocturnal enuresis.

in blood pressure beyond normal limits was recorded during treatment.

Discussion

DDAVP is a conveniently administered and effective drug for nocturnal enuretics, particularly when used with simple measures such as the avoidance of a large fluid intake before bedtime. However, early relapse of bedwetting does occur after withdrawal of DDAVP and our patients are a subgroup who have required regular DDAVP therapy to remain dry at night. We were concerned to establish whether DDAVP causes depression of endogenous ADH secretion similar, for example, to that produced in the pituitary-adrenal axis following prolonged administration of adrenocorticoids. The water deprivation test provides a simple, non-invasive and cheap indirect assay of endogenous ADH axis function without the need for a direct ADH radio-immunoassay.

Our results indicate that the regular use of DDAVP in these young patients does not have a significant effect upon endogenous ADH secretion or upon the other haematological, biochemical and hormonal parameters examined in the study. This supports previous findings that the drug is safe in short-term use and it also appears to be well tolerated and free of side effects in the longer term. The definitive role of effective DDAVP therapy in the management of refractory nocturnal enuresis remains to be established, however, especially with respect to the timing of surgical procedures such as bladder transection (Hindmarsh *et al.*, 1977) or enterocystoplasty (Bramble, 1982).

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Histological Changes in the Urinary Bladder Secondary to Urethral Catheterisation

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Summary—The macroscopic and microscopic features of the urothelial response of the human urinary bladder to urethral catheterisation are described. The catheter reaction is characterised by a predominantly eosinophilic inflammatory response producing, macroscopically, a papillary mucosal appearance termed polypoid cystitis. The severity of the epithelial inflammatory response correlates significantly with the duration of catheterisation. Urothelial dysplasia confined to the catheter reaction site was noted in 6% of cases. The possible implications of these findings are discussed.

The cytoscopic appearances of the urothelial response to the irritative effects of an indwelling urethral catheter are well recognised by urologists. Indeed, it is perhaps because of this familiarity that there have been relatively few histopathological descriptions of the catheter reaction in the literature (Ekelund *et al.*, 1983). The macroscopic differentiation of a catheter reaction from a papillary transitional cell carcinoma can be extremely difficult, if it were not for the preceding history of catheterisation. This difficulty was remarked on by Friedman and Ash (1959), who first described polypoid cystitis, a term subsequently used by Ekelund and Johannson (1979) to describe the histopathological changes of the catheter reaction. Recent concern over the toxicity of catheter eluates (Talja *et al.*, 1985) and the carcinogenic potential of the irritative effect of urethral catheters (Murphy *et al.*, 1986) prompted this investigation. A prospective study of 30 consecutive catheterised patients undergoing transurethral prostatectomy was conducted. A possible role for catheter-induced urothelial hyperplasia in urothelial carcinogenesis is discussed.

Patients and Methods

All 30 patients entered into the study had been catheterised for acute retention of urine secondary to benign prostatic hypertrophy. Their mean age was 73 years (range 58–84). They had been catheterised for between 2 days and 3 years, often with a variety of Silastic and latex rubber catheters. The catheters were removed on the morning of surgery and a catheter specimen of urine sent for bacteriological examination.

Cystoscopic evaluation of the catheter reaction was performed prior to transurethral prostatectomy. The severity of the reaction was graded as mild, moderate or severe. The site of the catheter reaction was recorded. Biopsies were then taken using cold-cup biopsy forceps (Storz) from the site of maximal reaction and from bladder mucosa elsewhere which, macroscopically, was most normal in appearance. Samples were randomly labelled A and B and the allocation recorded in the operation notes.

Paraffin-embedded 5μ sections of the biopsies were stained with haematoxylin and eosin and Perls' stains. Histological examination of the samples was performed without the observer knowing details of site, cystoscopic findings or the duration of preceding catheterisation. The severity of the mucosal inflammatory reaction was graded using a semiquantitative scale where 0 = none, 1 = focal lymphocytic infiltration, 2 = diffuse predominantly lymphocytic infiltration, 3 = diffuse predominantly eosinophil polymorphonuclear infiltration and 4 = grade 3 changes in combination with intra-epithelial eosinophilic micro-abscesses. The histo-

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pathological grades were correlated with the duration of catheterisation (days) using the Wilcoxon rank sum test and with the presence or absence of associated bacterial infection using Student's *t* test.

Results

The cystoscopic appearances were graded as severe in 11 cases (37%), consisting of a raised, oedematous, haemorrhagic papillary mucosal abnormality most prominent on the posterior bladder wall and often involving adjacent surfaces of the collapsed bladder. The reaction was mild or absent in 3 patients (10%) and moderate in 16 (53%).

Histological differences between the two biopsies (A and B) were noted in 26 patients (86%); "normal" mucosa was abnormal in 8 patients (26%) with the appearances of acute on chronic cystitis. Low power microscopy of the severe catheter reactions revealed broad-based, oedematous mucosal papillae conforming to the classical description of polypoid cystitis (Fig. 1). The catheter reaction consisted of a mucosal inflammatory response rich in eosinophil granulocytes in 26 patients (86%) with intra-epithelial micro-abscesses in 9 patients (30%) (Fig. 2). Urothelial hyperplasia was present in 11 patients (36%). Moderate urothelial dysplasia, confined to the biopsy taken from the area of maximal reaction, was present in 2 patients (6%), both of whom had been catheterised for >4 months (122 and 146 days) (Fig. 3). Acute inflammatory changes were absent in 3 patients (10%); iron-laden macrophages in the lamina propria, indicating previous haemorrhage, were found in 2 patients (6%). Neither urothelial necrosis nor squamous metaplasia was identified in any of the biopsies.

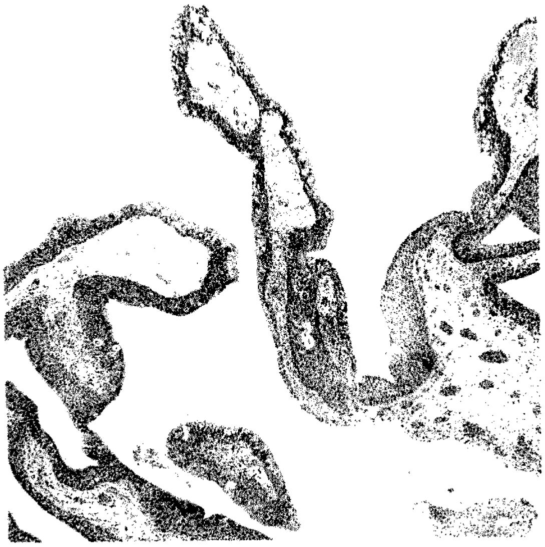

Fig. 1 Polypoid cystitis. (H and E ×33).

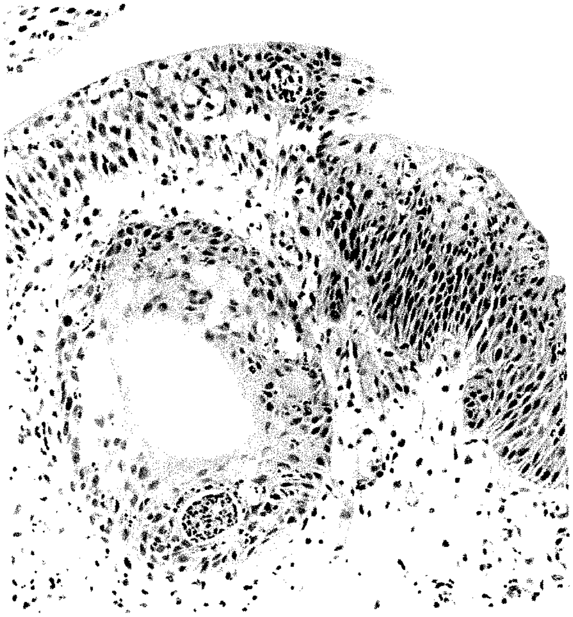

Fig. 2 Bladder urothelium showing epithelial hyperplasia, cystitis cystica and intra-epithelial eosinophilic micro-abscesses. (H and E ×360).

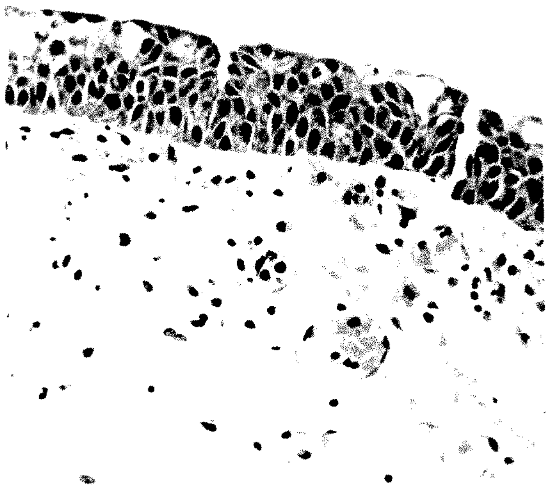

Fig. 3 Urothelium showing moderately severe urothelial dysplasia. (H and E ×250).

There was a statistically significant correlation between the grade of mucosal inflammatory response ($>$grade 2 *vs* $<$grade 3) and the duration of catheterisation ($P<0.05$). No patient who had been catheterised for less than 1 month showed evidence of intra-epithelial micro-abscesses (grade 4). There was no correlation between the severity of the mucosal inflammatory response and the presence or absence of associated bacterial infection. There was a good correlation between the cystoscopic appearances and the histological findings; of the 11 patients with a severe reaction on cystoscopic assessment, 9 had grade 4 and 2 had grade 3 urothelial inflammatory changes.

Discussion

The catheter-associated urothelial histological changes described in this series were very similar to those described as polypoid cystitis by Ekelund and Johannson (1979). However, they did not comment on the presence of eosinophils in the inflammatory response, which was described as consisting of neutrophils, lymphocytes and inflammatory cells. Indeed, the abundance of eosinophils in the urothelial inflammatory response, secondary to the stimulus of catheter irritation, has previously been reported only in animal experiments. Talja *et al.* (1985) noted an inflammatory infiltrate, consisting of 80% eosinophil polymorphs, around strips of catheter material implanted into the dorsal muscle of rabbits for 4 days. The marked eosinophilia of the catheter reaction in humans is almost certainly due to the presence of mast cells in the lamina propria of the urinary bladder mucosa. Following surface IgE-mediated antigenic stimulation, mast cells degranulate and release acidic tetrapeptides which attract and immobilise eosinophils (Holgate, 1983). Furthermore, in our study, the severity of the epithelial response correlated with the duration of catheterisation. In effect, therefore, the predominantly eosinophilic infiltration occurs after an initial lymphocytic response, reaching a peak approximately 4 weeks after catheterisation.

This feature is similar to the intestinal mucosal response to parasitic infection (Roitt *et al.*, 1985) in which there is an initial sensitising period of 2 to 3 weeks following exposure of the non-toxic parasitic antigens. These antigens stimulate T cells and macrophages to interact with B cells producing IgE-specific antibody. Both IgE and mast cell precursors then accumulate in local lymph nodes. The mast cells then acquire parasite antigen-specific IgE on their surface and return to the mucosa, where they degranulate on contact with the antigen, releasing the eosinophil chemotactic factors. In the case of the urothelial response the analogous antigen may well be the catheter substance. Furthermore, there was no correlation between the presence or absence of associated bacterial infection and the severity of the urothelial inflammatory response. This confirms the findings of Ekelund and Johannson (1979), who noted that the severity of the polypoid cystitis was not influenced by bacterial urinary tract infection. Catheter-associated polypoid cystitis, therefore, appears to be a direct response of the mucosa to the catheter *per se*, probably following a period in which an immunological response is mounted against catheter-derived antigens.

The chronic irritative effect of indwelling urethral catheters in rats has been shown to be a strong stimulus for the induction of urothelial neoplasia (Murphy *et al.*, 1986). The constant irritative action on the urothelium may have a promotor-like effect of inducing urothelial hyperplasia, identified in 36% of cases in our study. Persistent hyperplasia would allow neoplastic growth of latent urothelial tumour cells, previously transformed by sub-threshold doses of urinary carcinogens. Just as epithelial hyperplasia in the early experimental stages of skin carcinogenesis was reversible (Hicks, 1980), so was the urothelial hyperplasia of the catheter reaction found to be reversible (Ekelund *et al.*, 1983). Indeed, Murphy *et al.* (1986) suggested a two-stage process of irritative urothelial carcinogenesis, with papillary hyperplasia being the first, potentially reversible, stage. The development of squamous cell carcinoma of the urinary bladder, arising in mataplastic squamous bladder mucosa, in association with long-term catheterisation is well recognised (Kaufman *et al.*, 1977; Locke *et al.*, 1985), with an incidence of 8 to 10% following catheterisation for at least 10 years. In the development of these tumours, however, the latent period before the hyperplasia becomes irreversible and the relationship of this change to the occurrence of squamous metaplasia have yet to be elucidated. The finding of dysplasia in association with the catheter reaction has not previously been reported and although the association is possibly coincidental, it is obviously of considerable importance in this context.

In conclusion, the acute catheter reaction is typically a localised polypoid cystitis characterised by an eosinophilic infiltrate secondary to what is presumed to be the toxic, irritative effects of urethral catheters. This reaction may also be partly mediated by an immunological sensitisation to the catheter substance. Catheter-associated urothelial hyperplasia and dysplasia are probably relevant to the development of bladder tumours in patients with long-term indwelling catheters.

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Terodiline in the Treatment of Children with Unstable Bladders

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Summary—A double-blind study of terodiline compared with placebo was performed in 58 children aged 6 to 14 years with urgency or urge incontinence. All had an unstable bladder at cystometry. A bladder regimen was emphasised during the study. Continence was improved according to micturition charting and a pad test in both groups. Terodiline at 25 mg/day, however, gave significantly better results than placebo. In patients with a subnormal bladder capacity (≤ 150 ml), a significant increase in capacity was recorded on cystometry during medication with terodiline but not with placebo.

The improved continence seen in the placebo group was probably due to the non-specific bladder training achieved by the child's increased awareness and adult involvement during treatment. The even better results attained in the terodiline group shows this drug to be a valuable adjunct to a bladder regimen in children with urge incontinence, particularly since no important adverse effects were noted during an 8-week period.

Urgency and urge incontinence are common disorders in childhood. The cause of these symptoms is an unstable bladder in the vast majority of cases. The aetiology of this condition is not known, but it is assumed that there is usually a persistence of the uninhibited infantile bladder. During recent years, it has become obvious that the treatment of choice is bladder rehabilitation, comprising a bladder regimen and sometimes also biofeedback (Maizel *et al.*, 1979; Hjälmås and Hellström, 1981; Nørgaard and Djurhuus, 1982; van Gool *et al.*, 1984; Hellström *et al.*, 1987). Many patients need supplementary pharmacological treatment for detrusor relaxation, but these drugs often produce intolerable side effects (Abrams, 1984). A compound with few such problems is terodiline (terodiline hydrochloride), a calcium-blocking drug with an added anticholinergic effect and a long half-life of about 60 h (Karlén *et al.*, 1982). This drug has been reported to suppress unstable detrusor contractions in adults (Ekman *et al.*, 1980; Macfarlane and Tolley, 1984; Klarskov *et al.*, 1986) and children (Elmér, 1984). The aim of this study was to evaluate the efficiency and safety of terodiline for children with unstable bladders confirmed by cystometry.

Patients and Methods

Between March 1984 and December 1985, 61 children aged 6 to 14 years who attended the outpatient department with urgency or urge incontinence were studied. Informed consent was given both by patients and parents. Diagnostic cystometry showed instability of the bladder defined as detrusor contractions during filling (International Continence Society, 1984) or a premature micturition contraction at a small bladder volume (Hellström *et al.*, 1987). Children with signs of neurogenic disturbance, urinary tract obstruction or uncoordinated micturition according to their history or flow-rate and cutaneous sphincter EMG measurements were not considered for the study. Children with bacteriuria during the preceding 3 months, constipation or encopresis, or patients treated with drugs with a possible effect on the bladder were not included

During the course of the study 2 patients were found to have unco-ordinated micturition and 1 a

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neurogenic bladder disturbance; they were therefore not included in the evaluation. The remaining 58 children (22 boys and 36 girls, mean ages 9.4 and 8.6 years respectively) all completed the study. Their body weight ranged from 18 to 60 kg (mean 32). Previous urinary tract infections were documented in 13 children, verified in 7 as acute pyelonephritis.

Eighteen children had undergone previous treatment. A bladder rehabilitation programme had been applied in 8, imipramine had been given in 6, emepronium in 1, hyoscyamine in 1 and terodiline for 10 days 6 months earlier in 1. One child had tried pelvic floor exercises. None of these treatments had resulted in clinical improvement.

A history of daytime incontinence was given by 55 children, 50 had a primary type of incontinence and 5 a secondary type with previous dry periods exceeding 6 months. In 46 there were incontinence episodes at least once a day, in 8 one or several times a week and in 1 once or twice a month; 3 children had a history of frequency and urgency without incontinence.

Experimental plan

The study was designed as a randomised, double-blind, 2-period cross-over trial preceded by a 2-week run-in period to establish base-line values for each patient and familiarise them with the experimental routine and subjective protocols. The patients were then allocated to 3 groups (Table 1). Medication consisted of placebo and terodiline tablets 12.5 mg, prepared, packaged and allocated chronologically to the children by the manufacturer (KabiVitrum, Stockholm, Sweden) according to a random-number table which was revealed at the end of the study. To reduce the risk of side effects, each medication period began with 1 tablet/day for 1 week followed by 2 tablets/day for 3 weeks. There was no wash-out period between each period.

The regimen began with information and training on how to gain bladder control, such as learning how to start voiding even if no desire to do so was felt. The children were asked to try to void at least 4 to 6 times per day. In addition they were to record the time of each voluntary micturition and incontinence episode throughout the study on a micturition chart, although only the charts from the last 7 days in each period were used for the evaluation.

Table 1 Patients and Medication

Patients		*Periods*		
Group	*No*	*Run-in* (*2 weeks*)	*First medication* (*4 weeks*)	*Second medication* (*4 weeks*)
1	26	None	Placebo	Terodiline
11a	18	None	Terodiline	Placebo
11b	14	None	Terodiline	Terodiline

One day toward the end of each of the 3 periods the patients completed a pad test (Hellström *et al.*, 1986) at home. Over a 12 h period, pads were changed every hour, sealed in plastic bags and brought to the hospital the following day to be weighed. At this visit urinary flow and post-voiding residual urine were measured and cystometry was performed. A subjective assessment of the medication was recorded as improved, unchanged or worse. Each patient was asked about side effects. Blood pressure and body weight were measured.

The statistical methods used were the Wilcoxon sign rank test and Fisher's permutation test for paired samples (Bradley, 1968). The P values were calculated assuming 2-sided tests and significance was set at the 5% level.

The study was approved by the Ethical Committee of the Medical Faculty of the University.

Results

The code revealed that during the first medication period 32 children received terodiline and 26 placebo (Table 1). The effect of the medication was evaluated by using the data from the first medication period compared with those from the run-in period.

Micturition chart

When compared with placebo, terodiline significantly reduced the number of incontinence episodes and daytime micturitions as well as increased dry days per week (Table 2, Fig.). Improvement was also noted in the placebo group.

Pad test

The pad test quantified micturitions and incontinence episodes per hour during a 12 h daytime

Table 2 Mean Change with the Run-in Compared with the First Medication Period according to the Micturition Chart

Parameter	*Terodiline* ($n=32$)	*Placebo* ($n=26$)	P
Incontinence episodes/day	−1.1	−0.3	0.001
Daytime micturitions/day	−2.1	−1.0	0.02
Dry days/week	+3.0	+0.7	0.003

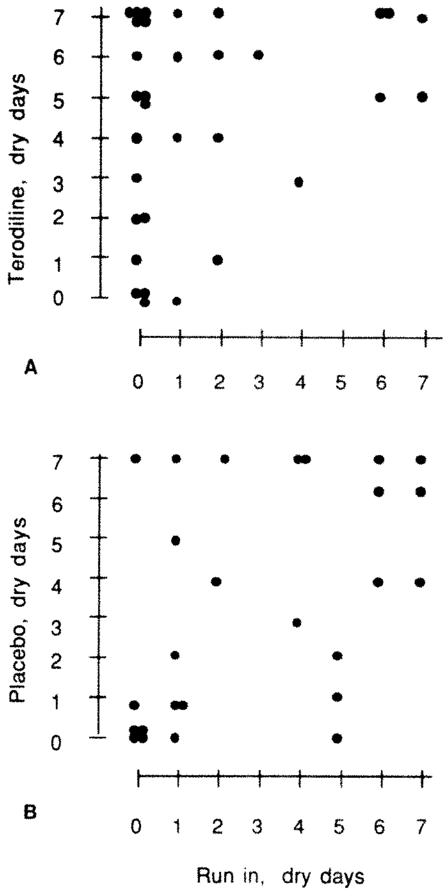

Fig. Number of dry days/week during first medication period plotted against run-in period for 32 children on terodiline (A) and 26 on placebo (B).

period. Significant changes, i.e. decreased number of micturitions, increased largest voided volume and decreased number of incontinence episodes were noted for the terodiline but not the placebo group (Table 3).

Cystometry

Children with a bladder capacity below 150 ml during the control period showed a significantly increased capacity during treatment with terodiline; this was not found in the placebo group (Table 4) or in the total material. The number of premature contractions during filling decreased in 17 and increased in 10 of 32 children in the terodiline group and did not differ significantly from the 25 investigated in the placebo group (16 and 8 respectively). Maximum pressure during micturition did not change during medication with either terodiline or placebo. There was no increase in residual urine in any of the groups during medication.

Table 4 Effect of Medication on Bladder Cystometric Capacity during First Period in Children with ≤150 ml Volume during Run-in Period

Patients			*Mean bladder capacity (ml)*		
Group	*Medication*	*No*	*Run-in*	*Medication*	*P*
I	Placebo	19/26	80	96	n.s
II	Terodiline	16/32	96	128	0.02

Subjective assessment of treatment

Improvement was reported by 27 of the 32 children treated with terodiline and by 18 of the 26 children given placebo; the groups did not alter significantly. No child indicated a worsening of symptoms.

Second medication period

During the second 4-week period, the patients retained improved continence both on continued terodiline and placebo treatment. The children who changed from placebo to terodiline showed further improvement and at the end of the second medication period there was no difference between the groups.

Adverse reactions

For evaluation of adverse reactions both medication periods were used. Four children reported side effects, all occurring during the first treatment period: 1 child on terodiline reported mild nausea; the other 3 were on placebo when reporting mild headache, moderate trembling and mild nausea.

Table 3 Pad Test Results during Run-in and Medication Periods (mean values and significance levels)

	Terodiline (n = 32)			*Placebo (n = 26)*		
	Run-in	*Medication*	*P*	*Run-in*	*Medication*	*P*
Number of micturitions	7	5	0.01	7	7	n.s.
Largest voided volume (ml)	160	202	0.02	145	158	n.s.
Number of incontinence episodes	2.6	1.7	0.05	1.5	1.6	n.s.

No child showed an increase in weight or blood pressure during the study.

Discussion

In the treatment of urge incontinence, anticholinergic drugs have been used extensively. However, side effects have often made adequate dosage difficult and limited the clinical usefulness of anticholinergics (Appelbaum, 1980; Ekman *et al.*, 1980; Abrams, 1984; Anderson, 1984). Drugs with a calcium-blocking effect also inhibit bladder contractions but they too have considerable side effects (Rud *et al.*, 1979; Palmer *et al.*, 1981). A combination of both anticholinergic and calcium-blocking effects should be favourable and is seen in terodiline (Andersson, 1984).

Previous studies in adults (Ekman *et al.*, 1980; Macfarlane and Tolley, 1984; Klarskov *et al.*, 1986) as well as in children (Elmér, 1984) have found terodiline to be effective in patients with urge incontinence and an unstable bladder. These findings were confirmed in this report. Clinically, terodiline was shown to give significantly better results than placebo. The placebo group, however, also showed a marked improvement, underlining the importance of an established regimen as a basis of treatment. Children with unstable bladders have probably adapted to the rebellious bladder by ignoring discrete and moderate signals and accept the necessity to void only when the first drops of urine are produced. If the drug is given without a regimen, there is a risk of an increase in the time interval between micturitions, with urge incontinence remaining unchanged. Such behaviour was noted in some children when assessing the micturition charts.

The most sensitive instruments for detecting improvement in bladder function seem to be the micturition chart and the pad test. Both methods call for the co-operation and interest of the children and for parental attention. In the pad test this attention need only span a single day, whereas, as used in this study, the micturition chart created a continuous interest in bladder function. The chart showed the children that bladder control was possible, thus improving self-esteem and a continued interest in staying dry.

Urodynamic studies of the effect of terodiline in children have not been previously reported. All 58 children were investigated on 3 occasions by standardised-cystometry (International Continence Society, 1984) but the findings were inconsistent. There were no differences after treatment between terodiline or placebo regarding the number of detrusor contractions or maximum pressure during micturition or a significant increase in bladder capacity. Since children with a normal capacity seem less likely to show an increase during treatment, children with a subnormal capacity ($\leq$ 150 ml) were analysed separately. In this group a significant increase in bladder volume was noted on medication with terodiline but not with placebo.

Since terodiline has such a long half-life (60 h) and no wash-out was carried out, it is difficult to use the second medication period to assess the efficacy of the medication. However, children on the active drug during the first period retained their improved continence at the end of the second period, regardless of whether this involved administration of placebo or terodiline.

An important result of this study was that adverse reactions were rare. Only 1 of the 58 children reported mild nausea during treatment with terodiline. On the other hand, 25 mg/day is not a high dosage and some subsequent patients have required a higher dose to achieve clinical improvement without having shown any adverse reactions. In conclusion we consider terodiline to be a valuable adjunct to a bladder regimen in children with urgency and urge incontinence caused by an unstable bladder.

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The "Plain Film" Bladder Shadow in Outflow Obstruction: as Accurate a Discriminant of Residual Urine as Ultrasound

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Summary—The height, width and area of the bladder shadow on post-micturition plain abdominal radiography was compared with the residual urine obtained at endoscopy from 58 men presenting with pure bladder outflow obstruction. Each parameter of the bladder shadow correlated significantly with the residual urine in patients in whom this shadow was visible. Post-micturition plain abdominal radiography is considerably cheaper than ultrasound and appears to be equally effective in the determination of residual urine. Its use as the sole imaging technique in the routine management of bladder outflow obstruction is recommended.

The volume of residual urine at operation has been shown to be the only significant factor predisposing to acute urinary retention (Powell *et al.*, 1980). A greater morbidity exists when transurethral resection of the prostate (TURP) is carried out in the presence of this complication of benign prostatic hypertrophy (Singh *et al.*, 1973). Traditionally, intravenous urography (IVU) has been used as a pre-operative discriminant of this residue. Recent studies with both "B" mode (Poston *et al.*, 1983; Beacock *et al.*, 1985) and real time ultrasound (Ravichandran and Fellows, 1983; Griffiths *et al.*, 1986) have suggested that they are as accurate as contrast radiology for this measurement. Whilst "B" mode ultrasound has limited application, doubt has been cast on the validity of real time scanning for this application (Hartnell *et al.*, 1987). This makes the adoption of out-patient bladder scanning (Vesey *et al.*, 1988) a dubious proposition for the evaluation of pure outflow obstruction. The plain abdominal film (KUB) has long been recommended as the only imaging necessary before "emergency" TURP (Marshall *et al.*, 1974), whilst the post-micturition bladder shadow from contrast studies has been shown to correlate strongly with direct measurement of residual urine (Griffiths and Castro, 1970; Abrams *et al.*, 1976). A prospective study was, therefore, undertaken to determine whether a pre-operative, post-micturition plain abdominal film was an accurate determinant of residual urine in men presenting routinely with pure bladder outflow obstruction.

Patients and Methods

A total of 58 adult male patients (aged 51–90 years) admitted from the waiting list of transurethral resection of the prostate were studied. None had microscopic or macroscopic haematuria, urinary tract infection or impairment of overall renal function as determined by a serum creatinine estimation. On the day of admission, 1 h after micturition, a plain abdominal film was taken using a standard radiological overcouch tube with a focus/film distance of 100 cm and an exposure of 70–80 Kv at 500 mA for 0.1–0.2 sec^{-1} on to Dupont Hi Plus film. The following day the patient micturated 1 h before induction of anaesthesia for lower urinary tract endoscopy. The residual urine was measured in ml at endoscopy. The height and width of the bladder shadow evident on the plain abdominal film were measured in cm, the height being taken from the superior border of the pubic symphysis to the maximal vertical height of the

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shadow and the width as the maximal transverse vesical diameter (Fig. 1). The area of the bladder shadow was determined by planimetry and expressed as cm^2. The patients were analysed as a whole and in 2 groups, 1 with a residual volume >150 ml and the other <150 ml. Correlation between the bladder shadow parameters and residual urine was made using standard least squares linear regression analysis.

Results

All patients completed the study. In 50 (86%) there was a visible soft tissue bladder shadow and in 8 (14%) this could not be discerned. The 50 patients with a bladder shadow evident had between 60 and 1800 ml (mean 317) of urine in their bladder at endoscopy; 15 (30%) of this group had a residue less than 150 ml (mean 102) and in 35 (70%) the residue exceeded this amount (mean 412). The 8 patients without a bladder shadow had between 25 and 150 ml of residual urine (mean 86).

By comparing the measured parameters of the bladder shadow and the residual urine in 50 men we were able to determine a linear relationship for height ($r=0.93$, $P<0.001$) (Fig. 2), width ($r=0.82$, $P<0.001$) (Fig. 3) and area ($r=0.89$, $P<0.001$) (Fig. 4). In the 15 men with less than 150 ml of residual urine there was no correlation with any of the parameters of vesical volume ($r=0.21$, $P=\text{NS}$ for height, $r=0.20$, $P=\text{NS}$ for width and $r=0.25$, $P=\text{NS}$ for area) and the mean percentage errors in this group were significantly higher (± 72.3 for height, ± 88.1 for width and ± 42.1 for area) than in the group with more than 150 ml in their bladder. In contrast, men with >150 ml of residual urine did have a significant correlation between residual urine and height ($r=0.93$, mean % error ± 9.8), width ($r=0.83$, mean % error ± 9.8) and area ($r=0.87$, mean % error 4.43). In this group, each of these parameters correlated significantly with the residual urine at the 0.1% level.

Discussion

The post-micturition urinary residuum has been considered the only important factor predisposing to acute urinary retention. It should determine some degree of priority for outflow tract surgery (Powell *et al.*, 1980). The means of measuring this residue without catheterisation has previously been by visual interpretation of the post-micturition film of the IVU or measurement of the parameters of bladder volume using various ultrasonic techniques.

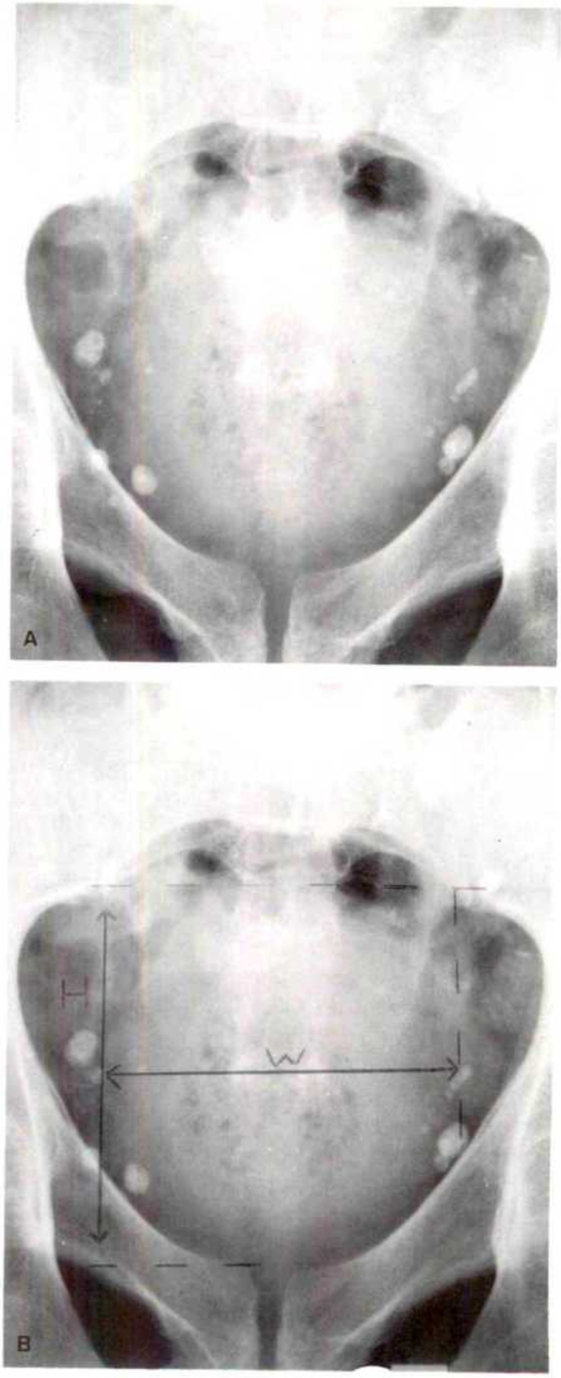

Fig. 1 (A) Plain film bladder shadow. (B) Method used to calculate the height (H) and width (W) of this shadow.

Intravenous urography is a technique with significant morbidity (1:3000) (Witten *et al.*, 1973) and mortality (1:75,000) (Hartman *et al.*, 1982) and now appears to have a limited place in the

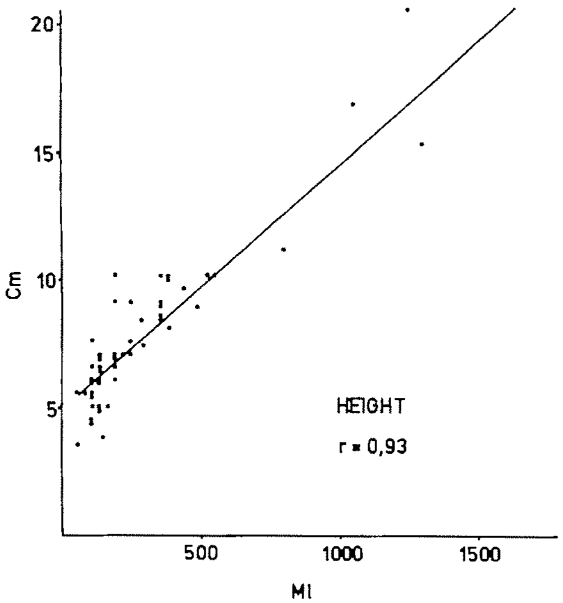

Fig. 2 Correlation between bladder shadow height (cm) and the residual volume (ml) in 50 males with pure bladder outflow obstruction

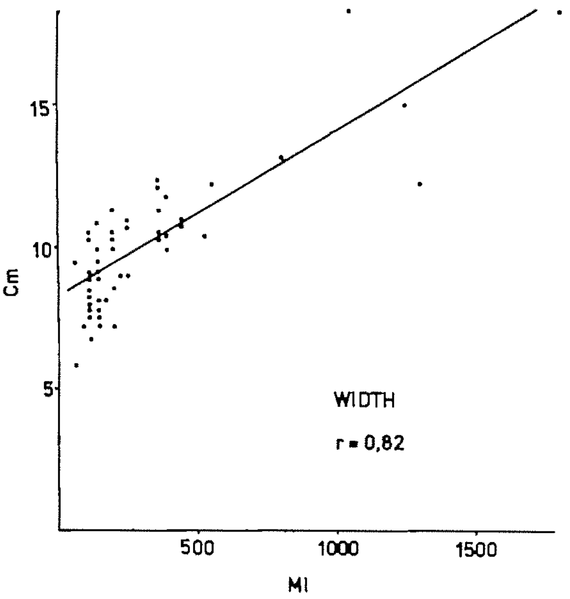

Fig. 3 Correlation between bladder shadow width (cm) and the residual volume (ml) in 50 males with pure bladder outflow obstruction

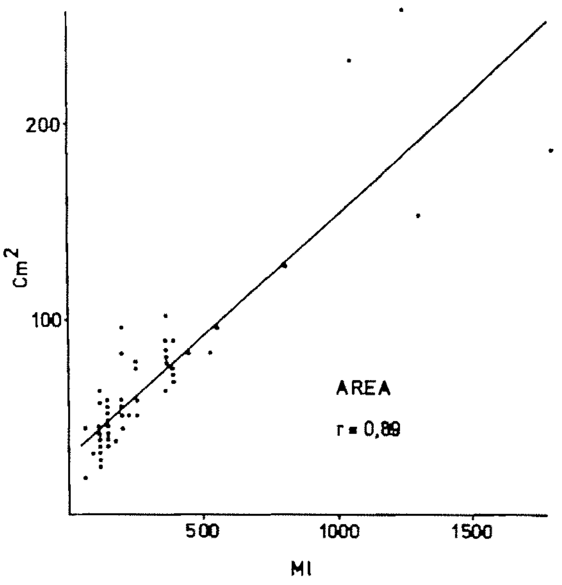

Fig. 4 Correlation between bladder shadow area (cm^2) and the residual volume (ml) in 50 males with pure bladder outflow obstruction

assessment of benign prostatic outflow obstruction. It has been shown to have a low pick-up rate for upper and lower tract abnormalities in the absence of haematuria, infection or compromised renal function (Christoffersen and Moller, 1981; Cascione *et al.*, 1987), it can increase in-patient waiting times before surgery (Marshall *et al.*, 1974) and have adverse economic effects on a urological service (Marshall *et al.*, 1974; Bauer *et al.*, 1980). Perhaps more importantly, it has been shown that many of the abnormalities determined by urography are either directly attributable to outflow obstruction and irrelevant to surgical management, or can be discovered by pre-operative urine culture, serum creatinine, a plain abdominal film and careful cystoscopy (Marshall *et al.*, 1974).

Real time ultrasonic evaluation of the urinary tract is conversely an effective method of examining the anatomy of both the upper and lower urinary tract (Vesey *et al.*, 1988) but has little impact on the patient's management in the absence of normal blood and urine investigations (Cascione *et al.*, 1987). Determination of the post-micturition urine volume with this equipment necessitates complex measurements of the bladder dimensions and the application of complicated formulae which can incur substantial errors, especially for volumes of less than 150 ml (Ravichandran and Fellows, 1983; Griffiths *et al.*, 1986). Observer variation is another significant source of error. Variations in micturition behaviour in the same patient may induce ultrasonic parameters that suggest significantly different residual volumes after sequential voids (Griffiths *et al.*, 1986). It has, however, been shown that by minimisation of these errors one can effect an ultrasonic accuracy of plus or minus 15% of the measured residual volume when this is greater than 150 ml (Griffiths *et al.*, 1986).

The plain abdominal film has been shown to be the only imaging necessary for the determination of urinary pathology before TURP for acute retention, primarily determining whether upper or lower tract calculus disease coexists with outflow obstruction (Marshall *et al.*, 1974). Abrams *et al.* (1976) have inferred that the post-micturition residue can also be determined from the bladder shadow in men presenting routinely with outflow obstruction. We have seen that there is significant correlation between the height, width and area of the soft tissue bladder shadow and the measured post-void residue for volumes greater than 150 ml in a similar group. Our data suggest that an absent bladder shadow probably indicates a residual urine of less than 100 ml; this may not indicate any predisposition to the development of acute urinary retention and does not involve any priority for TURP (Powell *et al.*, 1980).

We have found that planimetric measurement of the area of the bladder shadow appears the least inaccurate method of determining the residual volume, but it is a time-consuming, labour-intensive technique when carried out without computer assistance. For practical purposes, therefore, we suggest that one simple measurement of the height of this shadow above the pubic symphysis gives as useful an indication of the residual volume as real time ultrasound. This is without the necessity for expensive equipment, complex calculations and multiple parameter sampling. We believe that the post-micturition KUB is the only imaging technique necessary for the pre-operative evaluation of males presenting with pure bladder outflow obstruction.

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Biocompatibility of Urinary Catheters. Effect on Complement Activation

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Summary—The ability of 2 brands of urinary catheters to activate the complement system *in vitro* as a marker of biocompatibility was investigated. Pieces of a silicone/latex catheter and an all-silicone catheter were incubated in human serum. Complement activation was tested in 2 enzyme immunoassays, one evaluating C3 activation and the other the terminal complement complex (TCC) formation. The silicone/latex catheter caused considerably more complement activation in both assays than did the all-silicone one. The findings are in agreement with previous results of tissue toxicity tests. The methods presented may prove valuable for the practical purpose of testing the biocompatibility of urinary catheters.

The usual complications following the use of indwelling urinary catheters are mechanical trauma, infection and stone formation. Urethral strictures induced by the use of latex catheters and combined silicone/latex catheters following open-heart surgery, major trauma and myocardial infarction have been reported (Ruutu *et al.*, 1982; Edwards *et al.*, 1983; Sutherland *et al.*, 1983). These strictures differ from the post-catheterisation type in affecting a greater length of urethra (Ruutu *et al.*, 1984). The stricture formation is assumed to be associated with catheter toxicity, when poor blood flow allows toxic substances released from the catheter to accumulate in the surrounding tissue (Wilksch *et al.*, 1983; Elhilali *et al.*, 1986). Tissue toxicity studies have demonstrated low biocompatibility in urinary catheters containing latex (Talja *et al.*, 1985). In animal studies with reduced local urethral blood perfusion, infiltration of inflammatory polymorphonuclear cells occurred when toxic catheters were implanted in the urethra, in contrast to the response when all-silicone catheters were implanted (Talja *et al.*, 1986).

Activation of the complement system leads to the generation of many biologically active fragments (Ruddy, 1985). Of these, the anaphylatoxins (C3a, C4a and C5a) cause accumulation of polymorphonuclear cells (Hugli and Müller-Eberhard, 1978). The pathogenesis of the catheter-induced inflammation is still obscure. The present study was designed to investigate a possible association between complement activation and the inflammation caused by the catheters.

Materials and Methods

Preparation of samples

The complement source was human serum collected from 6 healthy members of staff (3 female and 3 male). The blood was left to coagulate for 30 min and then centrifuged for 10 min. The serum fractions were pooled and kept at 4°C until the start of the experiment. Inhibition of complement activation was obtained by adding fresh serum to glass tubes with ethylendiamintetra-acetic acid (EDTA) to a final concentration of 10 mmol/1.

Two brands of urinary catheters were investigated, a combined silicone/latex catheter with a main component of latex (identical to brand 3 in the study by Ruutu *et al.* (1985); personal communication) and 1 an all-silicone catheter. The catheters were delivered sterile and handled under clean conditions; 20 catheters of each brand were used. They were cut in small uniform pieces, each with a

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surface area of approximately 24 mm^2; 5-ml sterile glass tubes were filled to the top with equal amounts of catheter pieces. The pieces were incubated with 3 ml of fresh drawn serum in each test tube at 20°C and the closed tubes were shaken every 15 min. Fresh serum without catheter pieces and EDTA serum with and without catheter pieces served as controls in similar test tubes. Thirty glass tubes were prepared for each catheter brand and, for the controls, a total number of 180 tubes. After 0, 1, 2, 4 and 8 hours' incubation, 1 ml was drawn from 6 tubes in each group, put into cryotubes (Teknunc, Roskilde, Denmark) and frozen instantly in liquid nitrogen. The samples were kept at −80°C to avoid further complement activation and tested within 4 weeks.

Analyses of complement activation products

Complement activation was assessed in 2 enzyme immunoassays (EIA) specific to neo-epitopes on activation products not expressed in native complement factors. One was specific for C3 activation products, thus evaluating the initial part of the complement cascade (Garred *et al.*, 1988). In brief, polystyrene plates were coated with a mouse monoclonal antibody (bH6) specific for a C3 neo-epitope expressed on C3b, iC3b and C3c, but not on native C3. A rabbit anti-human C3c antiserum (Behring, Marburg, FRG) was used in the second antibody layer. Finally, a peroxidase conjugated anti-rabbit Ig was added (Amersham International, UK). The substrate was 2,2′-azino-di-(3-ethyl-benzthiazoline sulphonic acid) (ABTS). The results were read on a Dynatech MR 580 and referred to a standard of zymosan activated serum defined to contain 1000 arbitrary units/ml (AU/ml). The results were analysed by an Apple 11 computer with a Dynatech Immunosoft program. The other assay detected the fluid phase terminal complement complex (TCC), SC5b-9 (Mollnes *et al.*, 1985). TCC is an indirect indicator of C5a release since it cannot be formed without activation of C5 and release of C5a. In brief, polystyrene plates were coated with a mouse monoclonal antibody specific for a neo-epitope expressed on activated C9. A rabbit anti-human C5 antiserum (Dakopatts immunoglobulins, Copenhagen, Denmark) was used in the subsequent antibody step. The rest of the assay was performed as described for C3 activation.

Statistics

The Friedman test was used for analyses of parameter changes by time for each catheter. The Kruskal-Wallis test was used for inter-group comparisons. The results are presented as median with interquartile range.

Results

C3 activation

Median C3 activation is shown in Figure 1. After 2 h there was a significant increase in C3 activation products with both the silicone/latex catheters and the all-silicone catheters ($P<0.01$), whereas no increase was seen in the serum controls ($P>0.01$).

After 8 h there was a significant increase in C3 activation products with both catheters as well as the serum controls ($P<0.01$). The silicone/latex catheter, however, had now caused a significantly larger C3 activation (median = 545 AU/ml, interquartile range 285–650) than the all-silicone one (median = 128 AU/ml, interquartile range 114–152) ($P<0.01$). The increase in C3 activation for both catheters was significantly higher than in the controls ($P<0.01$).

There was no increase in C3 activation products in the EDTA containing controls incubated with the catheters.

TCC formation

Median concentrations of TCC are shown in Figure 2. After 2 h there was a significant increase in TCC concentration compared to baseline only with the silicone/latex catheter ($P<0.01$), but after 4 h the TCC concentration increased significantly in both the catheters and the serum controls ($P<0.01$). However, the TCC concentration was significantly higher with both of the catheters than in the control experiments ($P<0.01$). The silicone/latex catheter brought about more TCC formation than did the all-silicone catheter ($P<0.01$) and with both of the brands the increase was significantly higher than that in the control experiments.

There was no TCC formation in the EDTA-containing controls incubated with the catheters.

Discussion

In the present study the ability of 2 different brands of urinary catheter to activate the complement system *in vitro* was investigated. In the C3 activation assay the serum in the test tubes containing pieces of combined silicone/latex catheters was substantially activated after 1 h compared with the serum incubated with all-silicone pieces. Between 4 and 8 h a significant increase in the slope of the curve representing silicone/latex catheters was seen, in

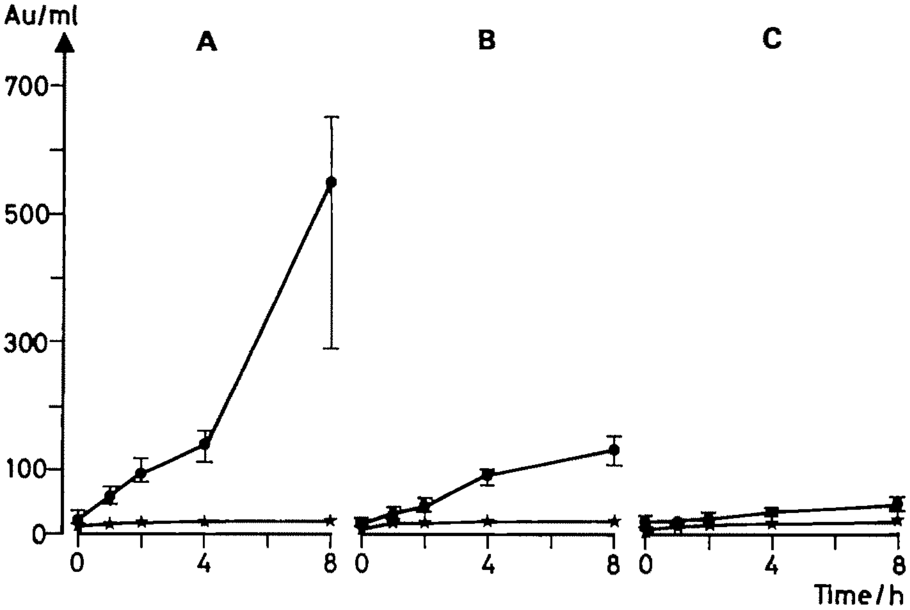

Fig. 1 C3 activation versus time from start of the experiment with 2 different brands of urinary catheter, 1 a combined silicone/latex catheter with a main component of latex (A), the other an all-silicone catheter (B) The control experiment without catheter pieces in the serum is shown in C. Median values and interquartile range are shown

●——● C3 activation, arbitrary units (AU/ml)

★——★ C3 activation (AU/ml) in controls containing EDTA

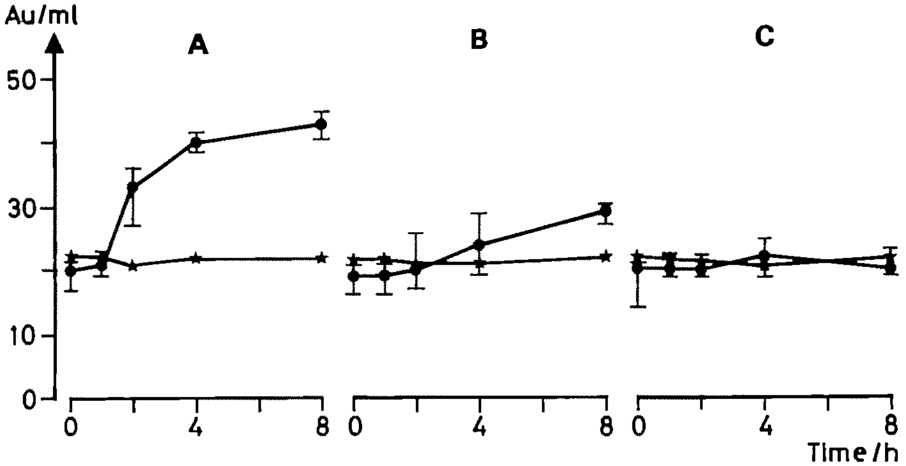

Fig. 2 Terminal complement complex (TCC) formation versus time from start of the experiment with 2 different brands of urinary catheter, 1 a combined silicone/latex catheter with a main component of latex (A), the other an all-silicone catheter (B) The control experiment without catheter pieces in the serum is shown in C Median values and interquartile range are shown

●——● TCC concentration, arbitrary units (AU/ml).

★——★ TCC concentration, (AU/ml) in controls containing EDTA.

contrast to the curve representing the all-silicone brand (Fig. 1). This phenomenon was not seen in the TCC experiment in which the curve showing the response to the silicone/latex brand reached a plateau after 4 h (Fig. 2). These results are in accordance with recent findings, which indicate that under certain conditions *in vitro* as well as *in vivo* a dissociation of the early and late phase of the complement cascade may take place (Mollnes, 1985a). The shape of the curves representing the all-silicone catheters was almost identical in the C3 activation assay and in the TCC assay. However, considerably less activation was found with the all-silicone brand than with the silicone/latex one. In the present study it was not possible to determine whether the complement activation was due to surface contact between complement and the silicone/latex surface only or was partly due to dissolving chemicals eluted from the silicone/latex pieces during the incubation.

Complement activation has previously been observed when blood has been in contact with artificial surfaces. Several authors have reported the occurrence of complement activation in patients during operations involving extracorporal circulation (ECC) (Chenoweth *et al.*, 1981; Jones *et al.*, 1982; Kirklin *et al.*, 1983). The ECC circuit itself may activate complement (Videm *et al.*, 1988). In dialysis the degree of complement activation seen was dependent upon the membrane applied. It appeared that complement activation was significantly higher with cuprophan membranes than with cellulose-acetate ones (Ivanovich *et al.*, 1983), whereas it remained almost entirely absent with polyacrylonitrile, polymethylmethacrylate and reprocessed cuprophan dialysers (Hakim and Lowrie, 1982; Hakim *et al.*, 1984).

After the initial report of the long anterior urethral strictures following open-heart surgery (Ruutu *et al.*, 1982), the aetiological factors involved have been the subject of considerable interest (Edwards *et al.*, 1983; Wilksch *et al.*, 1983; Ruutu *et al.*, 1985; Elhilali *et al.*, 1986). The tissue reaction caused by different catheter materials has been extensively studied (Goodpasture *et al.*, 1982; Wilksch *et al.*, 1983; Talja *et al.*, 1985). Apart from open-heart surgery, these strictures have been reported only sporadically (Syme, 1982; Edwards *et al.*, 1983). These cases, however, were also associated with hypovolaemic periods. Destruction of microvilli and holes in cell membranes was seen in scanning electron microscopy (SEM) when urinary catheters were implanted in hypoperfused animals. Latex catheters induced these changes deep into the epithelium, in contrast to silicone catheter experiments in which only superficial lesions were found. The epithelial changes seen in SEM may be a direct toxic effect on cells due to chemicals dissolving from the catheters and accumulating in the tissue during reduced blood flow (Talja *et al.*, 1986). This is in agreement with *in vitro* cell culture cytotoxicity tests (Wilksch *et al.*, 1983; Graham *et al.*, 1984; Ruutu *et al.*, 1985). As a result of the epithelial lesions the latex surface might come into contact with blood and lymph in the subepithelial space, in contrast to the silicone surface, which would still be surrounded by the urethral epithelium.

Destruction of the epithelium and the subsequent inflammatory reaction have been observed only a few hours after implantation (Talja *et al.*, 1986) but the mechanism which induces the inflammatory reaction is not known. It is well known that complement activation products may lead to activation and aggregation of polymorphonuclear inflammatory cells (Jacob *et al.*, 1980). The migration of polymorphonuclear neutrophils into the area in which complement has been activated represents the initial phase of a process that leads to demolition followed by organisation of the injured tissue with subsequent replacement of necrotic tissue by fibrous scar (Edwards *et al.*, 1983). The data presented here are consistent with the observation of an accumulation of leucocytes in the inflamed male urethra due to toxic catheters. This accumulation of inflammatory cells might be mediated by complement activation. Further studies are necessary to test the effect of various coated urinary catheters on the complement system. Moreover, eluates containing chemicals from the catheters are necessary to show whether they by themselves may activate the complement system.

The present tests for complement activation require no separation procedures prior to testing, in contrast to conventional tests (Wagner and Hugli, 1984; Mollnes, 1985b). Thus the methods used here are simpler and more reliable and might be helpful in evaluating the biocompatibility of synthetic materials in general.

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The Dissolution of Urinary Mucus after Cystoplasty

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Summary—Three agents have been tested for mucolytic activity to prevent or treat difficulties in bladder emptying following augmentation and substitution cystoplasty, particularly in patients emptying by intermittent self-catheterisation. Carbocysteine produced precipitation of mucus, which was found not to be helpful. N-acetylcysteine and urea both dissolved mucus, but urea proved to be more effective.

The use of bowel segments within the urinary tract is increasing as lower urinary tract reconstruction becomes more popular. Once incorporated into the urinary tract, bowel segments continue to function as they did in their natural site and one of the results of this, indeed the only clinically overt result, is the presence of mucus within the urine. This amounts to about 37 g/day (Murray *et al.*, 1987).

The presence of mucus in the urine is not usually a cause for concern, particularly if the patient is voiding spontaneously and the outflow tract is unobstructed. After lower urinary tract reconstruction, however, many patients rely on intermittent catheterisation to empty and this applies even more to patients who have had continent urinary diversions including the Kock pouch (and its variants) and the Mitrofanoff procedure.

When intermittent catheterisation is required, the calibre of the drainage channel is substantially less than that of the unobstructed "natural" bladder outflow of those patients who are voiding spontaneously. Difficulties with bladder emptying and problems of mucus retention are therefore much more common. The aim of this study was to test the efficiency of 3 known mucolytic agents in dealing with problems of this nature.

Materials and Methods

Urine was collected from patients with substitution cystoplasties and strands of mucus were extracted manually with a metal hook (Fig. 1) immediately following completion of the collection. The mucus was then incubated with the test solution in test tubes in a 37°C water bath on a moving platform.

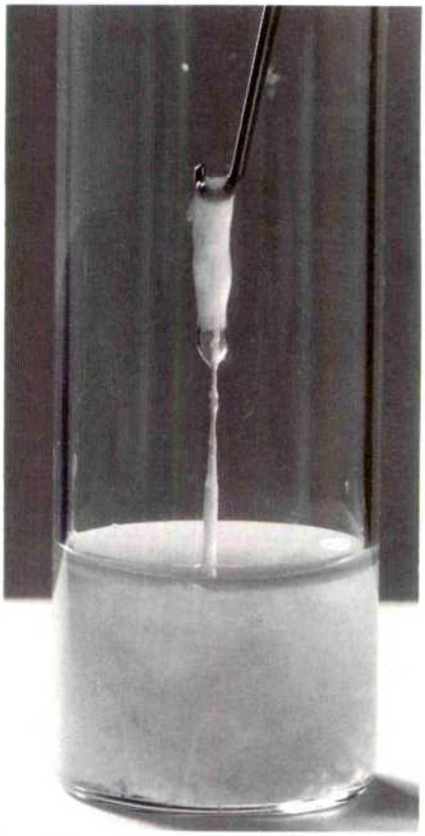

Fig. 1 Mucus extracted from urine with a metal hook.

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N-acetylcysteine (Parvolex) (Duncan, Flockhart & Co. Ltd, Greenford) was tested as a 20% w/v aqueous solution added to 1 g wet weight of mucus extracted as above, in 100, 200 and 400 mg concentrations.

Carbocysteine (Mucodyne) (Rorer Pharmaceuticals, Eastbourne) was tested in 2 forms: firstly as a powder obtained from capsules of 200, 375 and 750 mg (diluted either in 3 ml filtered urine or water) added to 1 g wet weight of mucus, and secondly in similar concentrations of the syrup form added to 1 g wet weight of mucus. Urea (BDH Chemicals Ltd, Poole) in anhydrous lyophilised powder form was added in concentrations of 0.4 g up to 4 g diluted in 3 ml filtered urine or water added to 1 g wet weight mucus.

Results

Carbocysteine in syrup form had no effect on the mucus in any concentration tested. Carbocysteine in powder form produced precipitation of the mucus to form a thick white sediment with a clear yellow supernatant (Fig. 2).

Urea dissolved the mucus completely at all concentrations tested above 0.5 g and its effect was evident after 30 to 60 min (Fig. 3). N-acetylcysteine dissolved (or more commonly dispersed) the mucus when used in a concentration of 200 mg or more (Fig. 3). This dissolution or dispersion took 2 to 3 h to occur at 37°C. It occurred much more slowly at room temperature. At a concentration of less than 200 mg N-acetylcysteine, mucus dissolution did not occur.

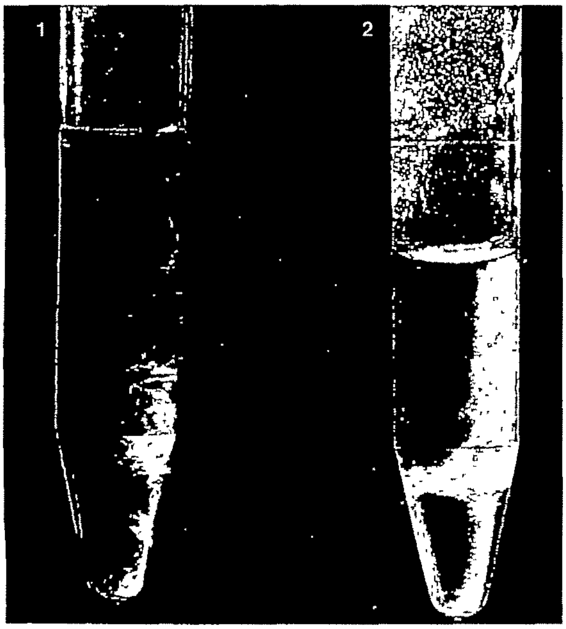

Fig. 2 Carbocysteine added to the urinary mucus Note the unaffected strands of mucus in tube No 1 and the thick sediment in tube No 2

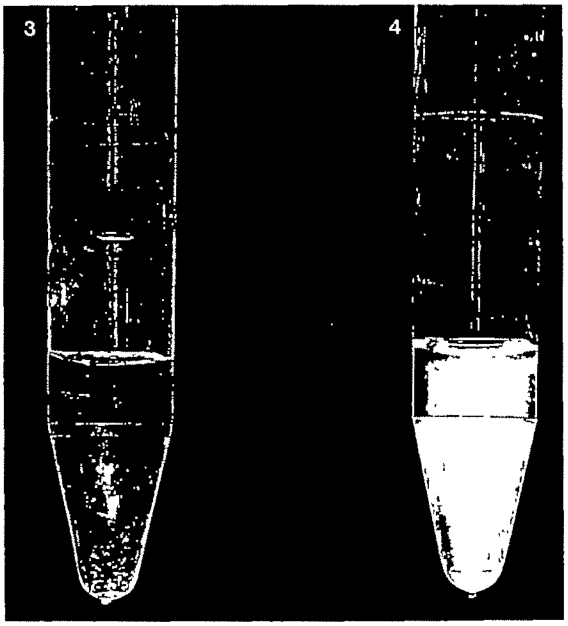

Fig. 3 Clear fluid in tube No. 3 following complete dissolution of mucus with urea Tube No. 4 shows cloudy fluid following dispersion/dissolution with N-acetylcysteine.

Discussion

Mucus is invariably present in the urine of patients who have had bowel segments incorporated into the urinary tract. It is not usually a problem unless the patient is dependent on intermittent catheterisation for bladder emptying, in which case blockage of the catheter can result, causing acute or chronic difficulties.

Mucus is a gel composed of macromolecules of glycoprotein. The backbone of these macromolecules is a long sequence of amino acids to which side chains of monosaccharides are attached. The glycoproteins in solution form a highly hydrated and expanded structure. This accounts for its physical property as a viscous material (Marriot, 1983). Carbocysteine is thought to exert its effect by attacking the secondary disulphide structure bonds (Martin *et al.*, 1980). Unfortunately the result was a thick sediment, so that although the drug was active, it was not helpful.

N-acetylcysteine, another cysteine derivative, reduces disulphide bonds through an interchange reaction (Sheffner, 1963). In the tests described above, it is effective, albeit after prolonged incubation. Its advantages, if used clinically, are that it is freely soluble in water, it does not depolymerise protein and has no action on fibrin or any other living tissue.

Urea is mainly used clinically as an osmotic diuretic agent. Waldron-Edwards and Skoryna (1966) first drew attention to its mucolytic properties, but its clinical use as such has been limited and sporadic. The mechanism of action may be attributed to the breakage of hydrogen bonds between the glycoprotein molecules. In our tests, however, it proved to have a marked effect in dissolving urinary mucus, and an effect that occurred much more rapidly and completely than was the case with N-acetylcysteine.

Hitherto, we have used acetylcysteine quite successfully as a bladder instillation in patients with emptying difficulties using intermittent self-catheterisation after a cystoplasty. In those with intermittent difficulty the solution is used as required; in those with regular difficulty the solution is instilled into the bladder after emptying by catheterisation last thing at night and left overnight. In both ways it has proved effective using 30 ml of a 20% solution. It would appear, however, *in vitro* at least, that urea is more effective if a source of clinical grade urea can be found.

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Effect of Atropine and Terbutaline on Motor Activity of the Continent Caecal Reservoir for Urine

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Summary—The effects of muscarinic receptor blockade (atropine) and of beta-adrenoceptor stimulation (terbutaline) on the motor activity of the continent caecal reservoir for urine were studied in 12 patients during continuous filling of the reservoir. Basal pressure was low at high level filling, but pressure waves with amplitudes of 40 to 50 cm H_2O occurred every other minute. The reservoir's functional adaptation, revealed as a diminished amplitude of pressure waves and evident soon after its construction, remained stable at long-term follow-up. Subcutaneously injected atropine or terbutaline did not influence the basal pressure but increased the volume at which the first pressure wave appeared and decreased the wave amplitude and frequency at high filling levels. Intra-reservoir instillation of these drugs did not alter the dynamic behaviour of the reservoir. In selected patients, orally administered anticholinergic drugs or beta$_2$-adrenoceptor agonists may be useful in the management of hyperactivity in a colonic segment used as a continent reservoir or bladder substitute.

Continent urinary diversion and substitution cystoplasty have been performed increasingly over the last 5 years, with receptacles for urine created from ileum, colon or a combination of the two and used as tubular or detubularised segments (Kock *et al.*, 1982; Goldwasser and Webster, 1985; Thüroff *et al.*, 1985; Månsson and Colleen, 1987). It is generally accepted that such receptacles for urine should ideally have a low intraluminal pressure. In the continent caecal reservoir the basal pressure is low but intermittent high pressure waves occur (Hedlund *et al.*, 1984). Concern has been expressed that these pressures may in time adversely affect renal function. In addition, high amplitude intermittent pressure waves may be a cause of reservoir outlet malfunction (Norlén and Trasti, 1978; Hedlund *et al.*, 1984). In a substitute bladder, low pressure is desirable for maintaining continence.

In this study we investigated the possibility of reducing the intraluminal pressure of the caecal reservoir with blockade of muscarinic receptors (atropine) or by beta-adrenoceptor stimulation (terbutaline). Atropine and terbutaline were injected subcutaneously or instilled directly into the reservoir.

Patients and Methods

The series comprised 10 men and 2 women aged 43 to 67 years (mean 56). They had undergone cystectomy and urinary diversion with a continent caecal reservoir 2 to 108 months previously (mean 58). Continence depended on an intussuscepted ileal nipple valve protruding into the caecal cavity or positioned within the distal part of the ileum (Månsson *et al.*, 1984; Månsson and Colleen, 1987).

Recordings of intra-reservoir pressure were made with the patient mildly dehydrated and in the supine position. All values were recorded during continuous filling of the reservoir with isotonic saline solution at 37°C via a baby-feeding catheter (8F) at a flow rate of 9 ml/min, using a mechanical pump. Filling was continued until the patient experienced fullness. The method has been described in detail by Hedlund *et al.* (1984).

The intra-reservoir pressure was first recorded before any drug was given (control value). The reservoir was then completely emptied and the

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filling procedure begun again 30 min later, 15 min after subcutaneous injection of 1 mg atropine (8 patients) or 0.5 mg terbutaline (7 patients). Pressure recordings were also made during continuous instillation into the reservoir (9 ml/min) of atropine (concentrations $3 \times 10^{-7} - 10^{-5}$M; 8 patients) or terbutaline (5.6×10^{-5}M; 4 patients). Finally, pressures were recorded during 2 consecutive reservoir fillings with no drug in 3 patients, to investigate the possible influence of repeat filling *per se*.

The variables measured were basal pressure at maximum filling volume (when the patient indicated the need to empty the reservoir), degree of reservoir filling when the first pressure wave appeared, and amplitude and frequency of pressure waves during the last 100 ml of reservoir filling. The pressures were registered via a silicone 7F catheter equipped with two microtransducers (series 16CT, Gaeltec) and the correct position within the reservoir was checked by identical responses to a Valsalva manoeuvre. Abdominal pressure was recorded as rectal pressure, by means of a balloon catheter connected to isolated pressure transducer amplifiers and a recorder (Linearecorder mark III, Watanabe).

The solutions and drugs were isotonic sodium chloride 9 mg/ml (Pharmacia), atropine sulphate 0.5 mg/ml (ACO, Sweden) and terbutaline sulphate 0.5 mg/ml (Draco, Sweden).

The statistical calculations were made with the Wilcoxon signed rank test and a probability level <0.05 was accepted as significant.

Results

When the caecal reservoir was full (400–600 ml) its basal pressure was low (Tables 1 and 2). Pressure waves with amplitudes of 40 to 50 cm H_2O occurred every other minute. The first pressure wave appeared at 100 to 200 ml of reservoir filling. Five patients had previously undergone identical recordings of intra-reservoir pressure (Hedlund *et al.*, 1984). Since then (observation periods up to 7 years), neither the amplitude of the pressure waves at high level filling (Fig.) nor the frequency and duration of the pressure waves had changed. Duplicated saline filling showed no difference in the dynamic behaviour of the reservoir in the 3 patients tested.

Effect of muscarinic receptor blockade

Subcutaneously administered atropine did not influence the basal pressure but increased the filling level at the first pressure wave and reduced the amplitude and frequency of the waves at high filling levels (Table 1). The instillation of atropine into the reservoir produced no significant change in the variables (Table 1). All patients reported slight tachycardia and dryness of the mouth after subcutaneous injection of atropine but there was no adverse reaction to intra-reservoir instillation.

Effect of beta-adrenoreceptor stimulation

Terbutaline injected subcutaneously also increased filling at the first pressure wave and reduced wave

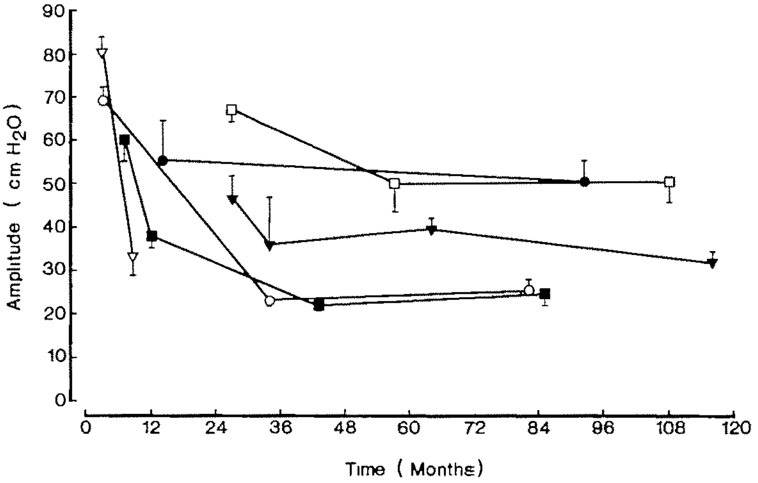

Fig. Changes in maximum amplitude of pressure waves in caecal urinary reservoir with time after reservoir construction (means ± SEM in 6 patients) Identical filling levels used for the comparison.

Table 1 Pressure Data from Caecal Urinary Reservoir at Continuous Filling before and after Subcutaneous Injection or Intra-reservoir Instillation of Atropine (means ± SEM)

	Basal pressure (cm H_2O)	*First pressure wave at (ml)*	*Pressure wave*	
			Amplitude (cm H_2O)	*Frequency (c/min)*
Pre-treatment control (n = 8)	14±2	130±25	52±11	0.5±0.05
Subcutaneous atropine (n = 8)	15±3	239±30†	29±5†	0.3±0.05*
Pre-treatment control (n = 8)	13±3	178±26	42±11	0.6±0.08
Intra-reservoir atropine (n = 8)	13±3	213±18	39±10	0.6±0.1

* $P<0.05$ † $P<0.01$

amplitude and frequency (Table 2). Direct instillation into the reservoir did not influence the variables (Table 2). Except for slight tremor after subcutaneous administration, no patient experienced side effects.

Discussion

The debate in recent years concerning bowel segments suitable for continent urinary diversion and bladder replacement has dealt mainly with pressure characteristics. Not only the part of the intestine to be used but also the configuration of the segment is important (Norlén and Trasti, 1978; Goldwasser *et al.*, 1987). The present study confirmed an earlier observation (Hedlund *et al.*, 1984) that functional adaptation of the caecal reservoir takes place and is manifest as reduced amplitude of the pressure waves. This change can be seen shortly after construction of the reservoir and thereafter the intra-reservoir pressure conditions remain stable (Fig.).

Table 2 Pressure Data from Caecal Urinary Reservoir at Continuous Filling before and after Subcutaneous Injection or Intra-reservoir Instillation of Terbutaline (means ± SEM)

	Basal pressure (cm H_2O)	*First pressure wave at (ml)*	*Pressure wave*	
			Amplitude (cm H_2O)	*Frequency (c/min)*
Pre-treatment control (n = 7)	17±4	108±18	50±13	0.5±0.07
Subcutaneous terbutaline (n = 7)	16±4	203±35†	39±11‡	0.4±0.09*
Pre-treatment control (n = 4)	14±6	135±35	41±7	0.7±0.2
Intra-reservoir terbutaline (n = 4)	12±5	225±21	39±7	0.6±0.1

* $P<0.05$ † $P<0.01$ ‡ $P<0.001$

It has been suggested that intermittent high intra-reservoir pressure (as in the caecal reservoir) threatens renal function by presenting functional obstruction to the flow of urine (Kock *et al.*, 1985). The glomerular filtration rate in patients with a caecal reservoir, however, was found to compare favourably with that in ileal or colonic conduit drainage (Månsson and Colleen, 1987). The effect of intraluminal pressure on the reservoir outlet is difficult to assess. Malfunction of the reservoir's intusscepted ileal nipple valve may arise from tension in the reservoir wall, tending to tear the two layers of the valve apart, or by a direct effect, causing extrusion of the valve. From reports on different types of reservoir it is difficult to deduce if the incidence of this complication differs. The intraluminal pressure of the detubularised ileal pouch is lower than that of the tubular shaped caecal reservoir. However, the clinical results suggest that technical experience in fashioning the reservoir outlet is the most important factor in obtaining satisfactory function (Skinner *et al.*, 1987). In substitution cystoplasty the dynamic properties may be more valid for the clinical outcome. It is vital that the pressure in the substitute does not exceed the urethral closure pressure. Thus, in bladder replacement it is imperative that low intraluminal pressure is maintained.

Muscarinic receptor stimulation has been described in various mammalian species to enhance the motility of the bowel (Bolton, 1981; Kirk, 1981; Scratcherd *et al.*, 1986). Atropine was shown to abolish spontaneous motility of the colon *in vitro* (Kirk, 1981) and *in vivo* (Scratcherd *et al.*, 1986). Hence it seems reasonable to expect that anticholinergic drug therapy will diminish the spontaneous motor activity of the caecal reservoir. In the present study, subcutaneously injected atropine increased the volume at which the first pressure wave occurred and lowered the amplitude and frequency of the recorded pressure waves. Atropine instilled directly into the reservoir did not have this effect. Parenteral administration is unsuitable for long-term therapy, however, and the disadvantages of oral atropine therapy are well known.

Intravesical or intra-reservoir instillation of drugs facilitates their concentration in the bladder or reservoir with avoidance of systemic side effects. Direct instillation of various drugs has been reported effective against detrusor hyperactivity (Öbrink and Bunne, 1978; Higson *et al.*, 1979; Gotoh *et al.*, 1986; Mattiasson *et al.*, 1987). In patients with a continent caecal urinary reservoir, the twice-daily instillation of 10 ml Lomotil (5 mg diphenoxylate hydrochloride, 0.05 mg atropine sulphate) reduced the frequency and amplitude of the pressure waves (Fowler *et al.*, 1987). In the present study, however, atropine instilled into the caecal reservoir (total amount approximately 3 mg) had no significant effect on the variables. The effect of Lomotil, therefore, was presumably due to diphenoxylate hydrochloride, which is considered to be a direct inhibitor of colonic peristalsis.

Beta-adrenoceptor antagonists were found to enhance colonic pressure in man (Abrahamsson *et al.*, 1983) and beta-adrenoceptor agonists might be expected to have a contrary effect. In the present study, subcutaneously injected terbutaline increased the filling at the first pressure wave and reduced wave amplitude and frequency in the caecal reservoir. The effects on the variables were of the same magnitude as those which followed atropine injection and, except for slight tremor, no side effects were apparent. Terbutaline instilled into the reservoir had no effect.

Our findings suggest that muscarinic receptor blockade and beta$_2$-adrenoceptor stimulation can reduce the motor activity of the caecal wall. Despite some side effects, in selected patients orally administered anticholinergic drugs or beta$_2$-adrenoceptor agonists may be useful in the management of hyperactivity in a caecal urinary reservoir or bladder substitute.

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Lack of Effect of Cholinergic Blocking and Alpha-adrenergic Stimulation on Nocturnal Incontinence After Ileocaecal Bladder Replacement

A Controlled Randomised Study

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Summary—A controlled randomised trial was carried out in 9 patients to examine the possibility of achieving nocturnal continence after ileocaecal bladder replacement by reducing the amplitude of the peristaltic contractions and by increasing the maximum urethral pressure pharmacologically. The trial consisted of 4 treatment periods, each of 2 weeks' duration: a single-blind placebo period was followed by 3 double-blind periods with phenylpropanolamine hydrochloride 50 mg *bd* (Kontexin), oxybutynin chloride 5 mg *tid* (Ditropan), and combined treatment. Each patient completed a frequency/volume chart before the trial and for the last 7 days of each treatment period. Filling and storage urethrocystometry was performed before treatment and at the end of each treatment period.

Treatment with phenylpropanolamine and oxybutynin failed to reduce the nocturnal urine leak of about 600 ml. Treatment did not influence the maximum urethral closure pressure, which remained unchanged at about 16 cm of water with the bladder substitute at rest and filled to its maximum cystometric capacity. At storage urethrocystometry, the treatment resulted in a decrease in the amplitude of the peristaltic contractions of about 10 cm of water to approximately 45 cm of water. Accordingly, the effect of alpha-adrenergic stimulation and anticholinergic suppression was found to be insufficient to achieve nocturnal continence in patients with ileocaecal bladder replacement.

With ileocaecal bladder replacement it is possible to retain urethral voiding and daytime continence after cystectomy (Gil-Vernet, 1962; Turner-Warwick *et al.*, 1967; Alcini *et al.*, 1985; Steven *et al.*, 1986) but almost all patients become incontinent by night. The nocturnal incontinence is a result of the peristaltic activity of the bladder substitute and the inability to increase the maximum urethral pressure during sleep (Jakobsen *et al.*, 1987). The present study was undertaken to see if nocturnal continence could be achieved by anticholinergic suppression of the peristaltic activity of the intestinal bladder and by alpha-adrenergic stimulation of the urethral sphincter area. The design of the study made it possible to evaluate the individual as well as the combined clinical and urodynamic effect of both treatments.

Patients and Methods

Nine patients with a median age of 66 years (range 53–72) completed the trial after informed consent. Each had undergone radical cystectomy and ileocaecal bladder replacement (Steven *et al.*, 1986). The median post-operative follow-up was 17 months (range 6–36).

The study comprised 4 treatment periods, each of 2 weeks' duration. The first was a single-blind placebo period. This was followed by 3 double-blind periods with active treatment. During each of these the patients received either (1) phenylpropanolamine hydrochloride (PPA) 50 mg *bd*, (2)

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oxybutynin chloride (OX) 5 mg *tid* or (3) both treatments. The treatments were given in random sequence and placebo tablets were given concurrently during periods (1) and (2). No washout was necessary between treatment periods because of the short half-life of PPA and OX (5.6 h (Lönnerholm *et al.*, 1984) and 3.3 h (Aaltonen *et al.*, 1984) respectively). Pulse and blood pressure were recorded at each visit.

Effects of Treatment

Frequency/volume urine chart

The patients completed a frequency/volume urine chart before the study started and for the last 7 days of each treatment period. They recorded the time of the urine voids and any episode of daytime incontinence. The volume voided at each micturition was recorded by 7 patients. The volume of urine leaked during sleep was recorded with a condom collecting device.

Urodynamic evaluation

The patients were examined immediately before the start of the study, at the end of the run-in period and at the end of each treatment period. Urodynamic assessment was made by uroflowmetry, determination of residual urine (Lo-Fric catheter, Astra Meditec, Denmark), medium-fill water urethrocystometry and storage urethrocystometry. Urethrocystometry was performed with the patient in a supine position using a 6F dual pressure sensor catheter (Dantec type 21 K 62, Denmark). Medium-fill cystometry was made with saline at 37°C and a filling rate of 50 ml/min. Storage urethrocystometry was performed for 30 min with the bladder substitute filled to its maximum cystometric capacity. A peristaltic contraction was defined as a sudden pressure rise of more than 10 cm of water. Measurements were made with the Urodyn 2100 (Dantec, Denmark). The methods, definitions and units conform to the standard recommended by the International Continence Society.

Statistical evaluation was made by a one-tailed Wilcoxon signed ranks sum test with a 5% level of significance. The interaction between the 2 drugs was evaluated by 3-way analysis of variance and for that purpose the values were logarithmically transformed when they were found not to be normally distributed (Dixon, 1983). To assess the precision of the statistical analysis we calculated for each variable the 95% confidence interval for the mean differences between the values recorded during the placebo and the treatment periods.

Results

Table 1 gives the glossary of symbols.

Frequency/volume urine chart (Table 2)

Treatment with OX and PPA did not reduce the nocturnal urine leak nor did it influence the 24-h urine output. Accordingly the ratio between the nocturnal urine leak and the daily urine output remained unchanged. Both OX and PPA induced a slight decrease in diurnal urinary frequency from approximately 8 to 7 and a corresponding increase in the voided volumes. Analysis of variance failed to demonstrate any interaction between treatment with OX and PPA. The confidence intervals of the mean differences in nocturnal urine leak and urinary frequency during the treatment periods were calculated at only ±23% and ±10% respectively.

Urodynamic studies

Urodynamic evaluation was performed in 8 patients; 1 refused instrumentation for urodynamic purposes.

Medium-fill cystometry (Table 3)

Treatment with both OX and PPA was associated with a significant increase in residual urine and in the maximum cystometric capacity. The resting pressure with the bladder substitute empty remained unchanged and so did bladder compliance. Therefore the resting pressure at maximum bladder capacity rose during treatment with OX. Both OX and PPA increased the bladder volume at which the first peristaltic contraction occurred. OX and the combined treatments produced small non-significant reductions in the amplitude of the

Table 1 Glossary of Symbols

Variable	*Unit*	*Symbol*
Residual urine	ml	res. urine
Bladder volume at first peristaltic contraction	ml	$V_{1\text{st contr}}$
Maximum cystometric capacity	ml	$V_{\text{cap max}}$
Resting pressure, empty bladder	cm water	$P_{\text{ves init}}$
Resting pressure at $V_{\text{cap max}}$	cm water	$P_{\text{ves cap max}}$
Maximum urethral pressure	cm water	MUP
Maximum urethral closure pressure	cm water	MUCP
Compliance	ml/cm water	C
Peristaltic contractions		
Maximum amplitude	cm water	$P_{\text{contr max}}$
Maximum duration	s	$t_{\text{contr max}}$
Frequency (amplitude > 10 cm water)	N/30 min	N

Table 2 Effect of Phenylpropanolamine Hydrochloride (PPA) and Oxybutynin (OX) on Nocturnal Incontinence and Urinary Frequency in 9 Patients and on Urinary Output and Volume Voided in 7 Patients after Ileocaecal Bladder Substitution

	Period				
	Run-in	*Placebo*	*PPA*	*OX*	*PPA+OX*
Nocturnal urine leak (ml)	594±276 (9)	670±299 (9) (NS)	590±269 (9) (NS)	606±307 (9) (NS)	536±284 (9) (*)
Urine output (ml/24 h)	2296±345 (7)	2315±612 (7) (NS)	2231±525 (7) (NS)	2297±509 (7) (NS)	2318±575 (7) (NS)
Urinary frequency (voids/day)	7.8±1.9 (9)	8.0±2.8 (9) (NS)	7.2±2.4 (9) (*)	7.0±2.5 (9) (*)	7.2±2.9 (9) (*)
Volume voided (ml)	218±46 (7)	205±58 (7) (*)	229±60 (7) (*)	282±168 (7) (*)	265±122 (7) (*)

(*). $P<0.05$ Values are mean ±SD/24 h The number of patients are given in parenthesis

Table 3 Effect of Phenylpropanolamine Hydrochloride (PPA) and Oxybutynin Chloride (OX) on Results of Medium-fill Water Cystometry in 8 Patients with Ileocaecal Bladder Substitutes

	Period				
	Run-in	*Placebo*	*PPA*	*OX*	*PPA+OX*
Res urine	0+0	1±2 (NS)	36±35 (*)	69±113 (*)	84±142 (*)
$V_{\text{cap max}}$	328±94	307±94 (NS)	353±103 (*)	421±110 (**)	376±64 (NS)
$V_{\text{1 st contr}}$	59±53	52±35 (NS)	112±131 (*)	129±65 (*)	184±118 (*)
$P_{\text{ves init}}$	11.3±4.5	10.5±4.4 (NS)	9.4±2.8 (NS)	10.0±4.2 (NS)	12.0±2.9 (NS)
$P_{\text{ves cap max}}$	24.6±10.8	19.5±6.7 (NS)	20.3±5.1 (NS)	23.3±2.0 (*)	24.1±5.8 (*)
$P_{\text{contr max}}$	61±21	54±23 (NS)	51±29 (NS)	48±15 (NS)	45±18 (NS)
C	46.7±54	41.5±22 (NS)	39.3±22 (NS)	34.1±12 (NS)	48.9±45 (NS)

(*): $P<0.05$ (**). $P<0.01$. Values are mean±SD. NS indicates $P>0.05$. A one-tailed Wilcoxon's signed rank sum test was used. The effects of placebo treatment were compared with the run-in values. The effects of PPA and OX given either alone or in combination were compared with the placebo values

peristaltic contractions. Analysis of variance showed no interaction between the 2 drugs.

Storage urethrocytometry (Table 4)

PPA failed to increase the maximum urethral pressure. Both OX and the combined treatments produced a significant decrease in the amplitude of peristaltic contractions of about 10 cm of water but the frequency of contractions remained constant. OX caused a significant increase in the duration of each contraction. No interaction between the 2 drugs was found. The confidence intervals of the mean differences recorded during placebo and treatment periods were as follows: $P_{\text{ves.}}$ ±29%, $P_{\text{contr. max.}}$ ±31%, $t_{\text{contr. max.}}$ ±20%, MUP ±31% and MUCP ±53%, respectively.

Side effects

No serious adverse effects were reported. PPA caused dizziness in 1 patient. OX caused a dry

Table 4 Effect of Phenylpropanolamine Hydrochloride (PPA) and Oxybutynin Chloride (OX) on the results of Storage Urethrocystometry at Maximum Cystometric Capacity in 8 Patients with Ileocaecal Bladder Substitutes

	Period				
	Run-in	*Placebo*	*PPA*	*OX*	*PPA+OX*
P_{ves}	17.3±7.5 (8)	14.9±5.8 (8) (NS)	16.0±5.5 (8) (NS)	21.6±6.0 (8) (**)	20.8±5.4 (8) (*)
MUP	30.1±6.4 (8)	31.7±14 (7) (NS)	36.0±9.7 (7) (NS)	38.0±6.7 (7) (NS)	35.5±6.5 (8) (NS)
MUCP	15.1±6.1 (8)	17.0±12 (7) (NS)	20.6±8.1 (7) (NS)	16.4±5.5 (7) (NS)	14.8±6.7 (8) (NS)
$P_{contr\ max}$	53±16 (8)	54±15 (8) (NS)	62±28 (8) (NS)	43±16 (8) (*)	45±9 (8) (NS)
$t_{contr\ max}$	42±10 (8)	46±15 (8) (NS)	49±16 (8) (NS)	56±16 (8) (*)	62±28 (8) (*)
N_{contr}	20±12 (8)	22±5 (8) (NS)	27±15 (8) (NS)	25±12 (8) (NS)	18±10 (8) (NS)

(*): $P<0.05$ (**): $P<0.01$. Values are mean ± SD. The number of patients are given in parenthesis. NS indicates $P>0.05$. One-tailed Wilcoxon's signed rank sum test was used. The effects of placebo were compared with the run-in values. The effects of PPA and OX given either alone or in combination were compared with the placebo values

mouth in 4 and the combined treatment caused a dry mouth in 6 patients. Blood pressure and pulse rates remained unaffected by all treatments.

Discussion

Nocturnal continence after ileocaecal bladder replacement was not achieved by anticholinergic and alpha-adrenergic treatment. The mean maximum urethral closure pressure ranged from 15.1 to 17.0 cm of water with the bladder substitute at rest and filled to its maximum cystometric capacity. To achieve continence the amplitude of the peristaltic contractions must not exceed this value. The mean amplitudes of the peristaltic contractions were 53 to 54 cm of water and could only be reduced by approximately 10 cm of water. Thus the effect of anticholinergic and alpha-adrenergic treatment appears to be quantitatively insufficient to achieve nocturnal continence after ileocaecal bladder replacement.

The confidence intervals of the differences in nocturnal leak during the placebo and treatment periods were narrow, so there is little probability that we may have overlooked a clinically important difference. The confidence intervals of the differences in mean urethral pressure and closure pressure were wide, which may account for our failure to establish a significant difference. Again it appears unlikely that we have overlooked an important difference because the absolute pressure differences were small.

The colon is innervated by the autonomic nervous system. Parasympathetic stimulation causes the release of acetylcholine, which acts to depolarise the smooth muscle cells and results in contraction (Kosterlitz, 1968; Schatzmann, 1968; Connell, 1986). Dilatation of the colon produces an increase in peristaltic activity, probably because it stimulates stretch receptors in its wall (Connell, 1986). Oxybutynin chloride suppresses smooth muscle contraction both as a result of its anticholinergic effect but also by a direct effect on the smooth muscle cell (Lish *et al.*, 1965). The administration of oxybutynin chloride, therefore, produced a decrease in the frequency of micturition and a corresponding rise in the volume of urine. The bladder volume at the first peristaltic contraction increased and the amplitude of the peristaltic contractions decreased, probably as a result of reduced sensitivity of the smooth muscle cell to reflex activity.

Phenylpropanolamine hydrochloride produced a small increase in residual urine and cystometric capacity. A slight reduction in the frequency of micturition was also obtained. This finding is in accordance with the expected action of the sympathetic nervous system on the motility of the colon (Bülbring and Kariyama, 1963; Daniel, 1968).

The proximal urethral sphincter mechanism, which contains a rich sympathetic innervation (Gosling, 1979) is excised during cystectomy and continence after intestinal bladder substitution is maintained by the distal striated sphincter with its somatic innervation (Gosling, 1979). This probably accounts for the failure of phenylpropanolamine hydrochloride to promote an increase in urethral pressure after cystectomy.

Because of the large 95% confidence intervals for MUP and MUCP, the lack of significant effect cannot be interpreted as meaning that there is no clinically important effect on these parameters. The number of patients may simply be too small. For the other variables, however, statistical precision is good and clinically important effects may be detected despite the limited size of the series.

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Evaluation of the Retrograde Contamination Guard in a Bacteriologically Challenged Rabbit Model

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Summary—We compared a newly developed closed urinary drainage system incorporating a retrograde contamination guard (RCG) with the conventional closed drainage system. The new system contains a solid bactericide (povidone iodine) pellet enclosed in a porous cartridge at the drain port of the urine collection bag. A catheterised rabbit model was used. The urine drainage bags were challenged daily for 8 days with an auxotrophically marked uropathogenic strain of *Escherichia coli* at the outlet tube. The bag urine was infected with the marked organism in 10 of the 11 rabbits in the control group (conventional collection bags) in 3.8 ± 1.03 days and in only 1 of the 13 rabbits fitted with the RCG. The RCG effectively prevents contamination of the urine drainage bag and thus may play an important role in reducing the incidence of nosocomial urinary tract infections.

Catheter-associated infections remain the most frequent and intractable problem in hospital infection control. Approximately 40% of all nosocomial infections are related to the urinary tract and are among the most common predisposing factors leading to fatal Gram-negative sepsis in hospitals (Schaeffer, 1986). Recent epidemiological studies have suggested that the acquisition of a urinary tract infection during indwelling bladder catheterisation is associated with almost a 3-fold increase in mortality among hospitalised patients (Platt *et al.*, 1982).

Following insertion of an indwelling urethral catheter, bacteria may ascend to the urinary tract either by extraluminal migration from the urethral meatus or by intraluminal migration following disconnection of the distal catheter-proximal drainage tube junction or contamination of the drainage bag (Schaeffer, 1986).

The popularisation of the closed drainage system in the 1960s has led to a decrease in the incidence of catheter-associated bacteriuria attributable to the luminal route (Kunin and McCormick, 1966; Finkelberg and Kunin, 1969). Several factors in a busy hospital can lead to contamination of the closed drainage system (Garibaldi *et al.*, 1974; Rutala *et al.*, 1981). This contamination spreads proximally, in the form of an adherent biofilm, along the inner surface of the lumen and continues to play an important role in catheter-associated bacteriuria (Maizels and Schaeffer, 1980; Nickel *et al.*, 1985a). We report our evaluation of the retrograde contamination guard in a catheterised rabbit model. The RCG device is fitted at the drain port of the urine collection bag and effectively prevents contamination of the urine bag in this bacteriologically challenged model.

Materials and Methods

A detailed description of the catheterised rabbit model used in this experiment has been published previously (Nickel *et al.*, 1985a). A series of 28 New Zealand male rabbits weighing 3 to 3.5 kg were randomly assigned to either the control or treatment group. Under suitable halothane inhalation anaesthesia an internal jugular central venous line was inserted by cut down and tunnelled subcutaneously to an exit site on the back. This allowed administra-

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tion of 5% dextrose and electrolyte solution at 60 ml/h to maintain a daily urine output of 1.2 litres. The rabbits were catheterised aseptically with a 10 F uncoated latex catheter after painting the perineal region with povidone iodine solution and draping. The catheter balloon was inflated. Half of the animals were fitted with a conventional drainage system and the other half were fitted with the RCG system. The rabbits were then placed in a specially designed restraining cage. The urine bag was suspended so that the top of the bag was approximately 45 cm below the rabbit urethra and not touching the floor.

The outlet tube of the urinary drainage bags was bacteriologically challenged each day by contaminating it with an auxotrophically marked uropathogenic strain of *E. coli* (lactose −ve, streptomycin resistant). The bacteria were stored at −70°C and were grown in nutrient broth (Difco) at 37°C for 8 h. The cultures were centrifuged, washed 3 times and resuspended in phosphate buffered saline (pH 7.2) to give 10^6 cfu/ml. The drainage bag was emptied 3 times daily. When the drainage bag was emptied for the first time each day the distal 0.5 cm of the outlet tube was placed in the bacterial suspension for approximately 2 s. Urine specimens were obtained from the drainage bags prior to their inoculation each morning. A solution of hydrogen peroxide (3%) and ethanol (70%) was used to sterilise the puncture site; 0.1 ml aliquots of the specimens were serially diluted and plated on agar plates and then incubated at 37°C overnight. Each dilution was replicated twice and the number of bacteria per ml reported as an average of these 2 values. The first dilution series was plated on nutrient agar plates; the other series was plated on McConkey agar with 100 μg per ml of streptomycin. The auxotrophically marked *E. coli* was easily distinguished using this technique. The experiment was terminated when the catheters were *in situ* for 8 days.

The onset of infection was defined according to Thornton and Andriole (1970) as the first day on which the causative bacterial species that eventually progressed to $>10^5$ cfu/ml could be recovered from the bag urine regardless of the initial colony count. Scanning electron microscopy (SEM) was used to study the inside surface of the urine bags in the rabbits infected with the marked *E. coli*. The bag material was prepared for SEM using the technique employed previously to examine bacterial populations growing in a biofilm (Nickel *et al.*, 1985b). The samples were examined using a Hitachi S450 electron microscope.

Results

Four rabbits were excluded from the study because of anaesthetic problems in 1, obstruction of the catheter lumen within the first 12 h in 1, and 2 rabbits chewed through their catheters; 24 rabbits completed the 8-day study without deviation from the study protocol. The study population consisted of 11 control and 13 experimental subjects.

The bag urine remained sterile in only 1 of the 11 rabbits in the control group. The marked *E. coli* first appeared in the bag urine in the other 10 subjects in 3.8 ± 1.03 (SD) days (range 2–5) and reached 10^5 cfu/ml in 5.3 ± 0.94 (SD) days (range 4–7). The marked *E. coli* was recovered from 1 of the 13 experimental group subjects on day 4 (Fig. 1), 3 of the remaining 12 rabbits in that group became infected with bacteria other than the challenge organism. These organisms, which were mainly Gram −ve rods, were also found on the outer surface of the urethral portion of the catheter, the outer surface of the catheter tip and the bladder urine, indicating that they had gained entrance to the urinary tract through the peri-urethral route (Fig. 2).

SEM of the bag material from the rabbits infected with the marked *E. coli* demonstrated the presence of a continuous biofilm in which rod-shaped bacterial cells were embedded in the amorphous residue of their exopolysaccharide glycocalices (Fig. 3). This biofilm gradually spread from the outlet tube to the urine bag.

Discussion

An indwelling urethral catheter is inserted in 10 to 15% of patients admitted to a community hospital (Kunin and McCormick, 1966; Finkelberg and

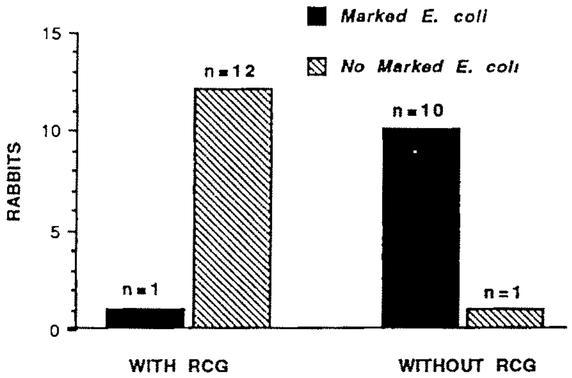

Fig. 1 Comparison between treatment and control groups regarding the recovery of the marked *E coli* used from the bag urine

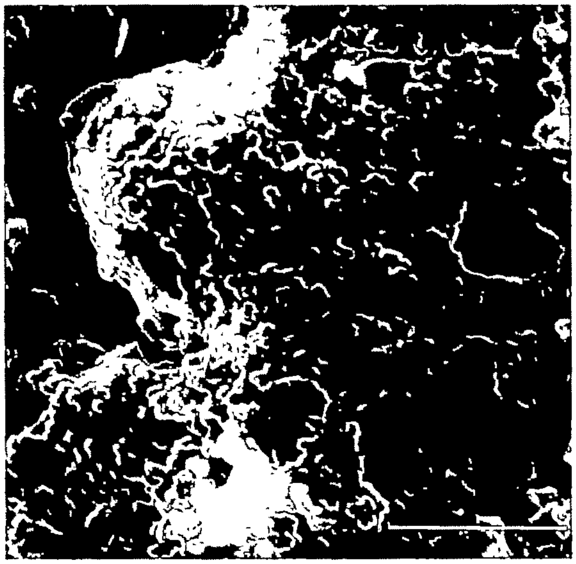

Fig. 2 Scanning electron micrograph of a critical point dried preparation of the outer surface of the urethral catheter in an animal infected with a contaminating Gram -ve organism. These organisms, growing in a biofilm, were seen spreading on the outer surface of the urethral portion of the catheter and the catheter tip and were cultured in the bladder urine. Bar = 5 µm

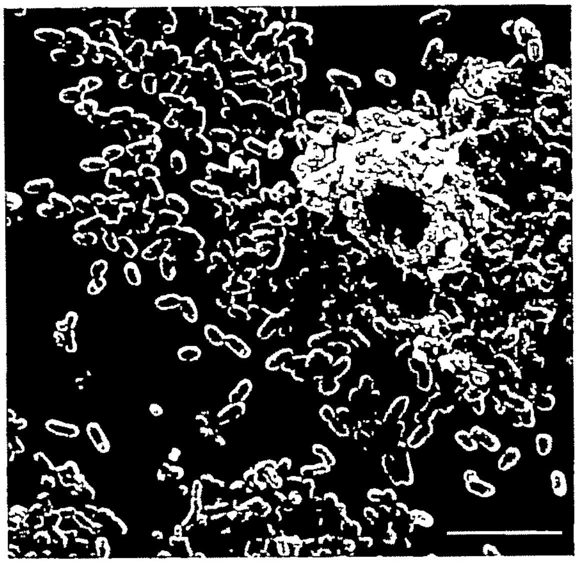

Fig. 3 Scanning electron micrograph of a critical point dried preparation of the inner surface of urine drainage bag in an animal infected with the marked *E coli* Note the almost continuous biofilm in which the rod-shaped bacterial cells are embedded in the thick exopolysaccharide glycocalix Bar = 5 µm

Kunin. 1969; Garibaldi *et al.*, 1980); 40% of nosocomial infections occur in the urinary tract and 75% of these patients have had some form of urological instrumentation, usually in the form of catheterisation before their infection (Martin and Brookrajian, 1962).

This problem has led to various attempts to reduce the incidence of urinary tract infections in catheterised patients, *e.g.* closed drainage systems (Kunin and McCormick, 1966; Thornton and Andriole, 1970), antibiotic irrigation of the closed drainage system (Warren *et al.*, 1978), daily meatal care and application of a topical antibiotic to the meatus (Butler and Kunin, 1968a; Burke *et al.*, 1981), systemic antibiotic (Butler and Kunin, 1968a), incorporation of antireflux valves, air locks and drip chambers into the drainage system and the addition of antibacterial agents in the urine bag (Maizels and Schaeffer, 1980). Not all of these modifications were successful.

The catheterised urinary tract is more vulnerable to bacterial colonisation. The organisms gain entry to the tract either through the peri-urethral route or through the luminal pathway from a contaminated urine drainage bag or as a result of disconnection of the catheter-proximal drainage tube junction (Garibaldi *et al.*, 1974; Schaeffer, 1986). We have previously demonstrated that once the infecting organism has gained access to the tract it develops an adherent biofilm that gradually spreads along the surface of the catheter, drainage tube and urine bag (Nickel *et al.*, 1985a). This mode of spread is not inhibited by antireflux valves, air locks or drip chambers installed in the closed drainage system. The biofilm-enclosed mode of growth was also shown to be very resistant to antibacterial agents (Nickel *et al.*, 1985b, c) and its exopolysaccharide glycocalix component has an inhibitory effect on the cellular and humoral components of the immune system (Gray *et al.*, 1984, 1987). This explains the difficulty encountered when attempting to treat a catheter-associated urinary tract infection or asymptomatic bacteriuria by systemic antibiotics (Butler and Kunin, 1968b), local antibiotics (Butler and Kunin, 1968a; Burke *et al.*, 1981) or antibiotic irrigation (Warren *et al.*, 1978).

In order to delay or prevent this seemingly inevitable catheter-associated bacteriuria the organisms must be prevented from gaining access to the system and adhering to its surface. The ascending intraluminal route was the primary source of infection in the era of open, non-sterile catheter drainage (Kunin and McCormick, 1966; Thornton and Andriole, 1970). Patients with contaminated bag reservoirs were at high risk; bacteriuria developed in over three-quarters of those who remained catheterised for at least 1 day after bag contamination had occurred. In each case the same organisms were cultured from the drainage bags and the infected urine. The importance of the ascending luminal route even with the use of closed drainage systems has already been described (Maizels and Schaeffer, 1980; Rutala *et al.*, 1981; Nickel *et al.*, 1985a).

Colonisation of the urine drainage bags of patients in reverse isolation or those on systemic antibiotics at the time of catheterisation occurs less frequently than in those of untreated patients on open wards (Schaeffer, 1982). Cross-contamination is less likely in the first instance and the bags contain bactericidal drug concentrations owing to systemic antibiotic therapy in the second (Schaeffer, 1986).

The patients at highest risk of developing catheter-associated bacteriuria appear to be those sharing hospital rooms with bacteriuric patients or other catheterised patients (Maizels and Schaeffer, 1980). Contamination of the urine bag outlet tube has been shown to occur when the terminal portion of the drainage tube comes in contact with a contaminated urine measuring container when the bag is emptied. This mode of cross-contamination has been implicated as a major mode of spread in an outbreak of nosocomial urinary tract infection caused by *Serratia marcescens* (Rutala *et al.*, 1981).

Maizels and Schaeffer (1980) demonstrated that maintenance of a sterile drainage bag by the addition of hydrogen peroxide significantly reduced the incidence of catheter-associated bacteriuria in patients with spinal cord injury who were on an open ward and received no systemic antimicrobial agents. However, this sytem required a secondary sterile drainage bag connected to the primary bag for the instillation of the hydrogen peroxide; these secondary bags were changed every 8 h therefore requiring nursing intervention and time and the added expense of 3 new bags per day for each patient.

The RCG system contains a solid bactericide (povidone iodine) pellet enclosed in a porous cartridge at the drain port of the urine collection bag. Urine solubilises the bactericide at the time of emptying of the collection bag. The concentrated bactericide pools in the chamber of the drainage tube and acts as a barrier to prevent bacteria from entering the bag. The solubulised bactericide does not reflux into the urine drainage bag and therefore does not interfere with the quantitative urine cultures obtained from the bags by puncture. The solid bactericide pellet is efficacious for 5 to 7 days (Fig. 4).

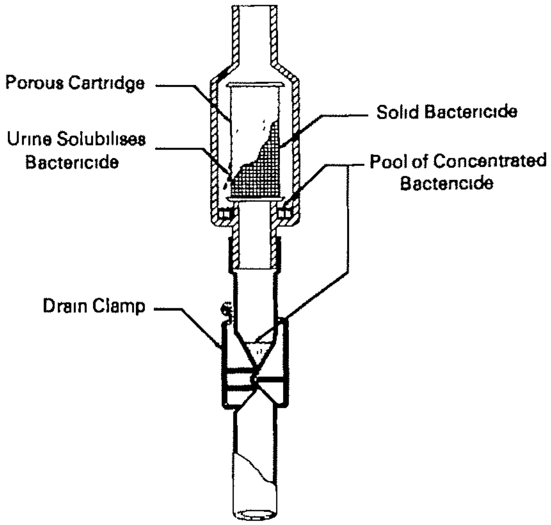
Porous Cartridge
Urine Solubilises Bactericide
Drain Clamp
Solid Bactericide
Pool of Concentrated Bactericide

Fig. 4 Diagrammatic representation of a longitudinal section of the RCG device

The system is self-contained, requires no nursing intervention and is not dependent on user compliance. The efficacy of the RCG in preventing contamination of the bag urine is evident from the results of this study. The marked *E. coli* contaminated the bag urine in only 1 of 13 animals in the treatment group in contrast to 10 of 11 rabbits fitted with conventional drainage system bags ($P < 0.005$). Although the predominant route of entry of organisms to the catheterised urinary tract is the periurethral route, the recovery of the marked organism in 10 of 11 bacteriologically challenged rabbits not protected by the RCG emphasises the importance of the intraluminal route should contamination of the drainage port occur in a busy hospital situation. The effective prevention of contamination of the urine bag demonstrated in this study eliminates a significant mechanism of cross-contamination and an important contributor to a continuing and intractable problem in hospital infection control.

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Effect of Suprapubic Operation on Urethral Closure

Evaluation by Single Cough Urethrocystometry

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Summary—To evaluate urodynamic effects of modified Burch colposuspension, 24 patients with stress urinary incontinence were investigated before and 6 to 9 months after the operation. A new method of urodynamic evaluation was performed using a multitransducer-catheter, 5 microtransducers inside the urethra and 1 in the bladder, connected to a computer and graphic plotter. Single coughs were analysed with the catheter in a fixed position and the patient in the standing position.

The operation, which was successful, in all but 1 patient, did not alter urethral pressure at rest, but urethral closure pressure at stress after the operation (mean 45.0 cm H_2O (SD 21.6)) was significantly higher ($P<0.005$) than the -3.6 cm H_2O (SD 10.2) recorded before the operation.

The pressure transmission ratio was less than 100% in 22 patients before the operation and more than 100% in 18 patients afterwards, the pre- and post-operative mean values being 78.9% (SD 11.9) and 109.5% (SD 17.2) respectively ($P<0.0005$).

Burch colposuspension markedly improves urethral closure function as evaluated by this method, which analyses the pressure data at different points of the urethra and bladder during one single cough.

The suprapubic Burch operation is widely used in the surgical treatment of stress urinary incontinence and has a failure rate of 2 to 27% (Mundy, 1983; Bhatia and Bergman, 1985).

To assess the urodynamic effects of such an operation we performed a thorough pre- and post-operative urodynamic evaluation of patients who had undergone this procedure.

We used our new computer-programmed urodynamic method (Kauppila *et al.*, 1988) which has several technical advantages over the old two-transducer method, *e.g.* fixed position of the catheter during the stress test and simultaneous registration of the pressure data from several urethral points; in addition only a few coughs are needed for registration of the pressure data Each transducer registers 300 signals/s, which gives a dynamic picture of urethrovesical pressure conditions during the single cough and enables a detailed record to be made of urethral closure function.

Patients and Methods

A series of 24 patients (median age 47.1 years, range 33–64; weight 68.4 kg, range 54–100) were investigated before the operation and 6 to 9 months afterwards.

In the pre-operative investigation the character and severity of incontinence was evaluated using the urgency score method (Kauppila *et al.*, 1982) (median 2.4, range 0–5), the standing stress test and urodynamic evaluation, which confirmed that each patient had pure stress incontinence: 8 patients had grade III incontinence, 13 had grade II and 3 grade I incontinence (Ingelman-Sundberg, 1951).

A modified suprapubic Burch operation was used (Tanagho, 1976; Bhatia and Bergman, 1985). Minimal dissection was carried out within 2 cm of the urethrovesical junction and urethra. The non-absorbable sutures (2 on both sides) were placed through the full thickness of the paravaginal fascia instead of the para-urethral tissues of the pelvic floor. The sutures were fixed to Cooper's ligaments.

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At the end of the procedure, the surgeon was able to place two fingers behind the pubic bone in front of the proximal urethra to ensure there was no kinking or compression of the urethra.

Urethrocystometry was performed by means of a catheter with 6 microtransducers (Honeywell, Best, Holland), a 6-channel amplifier (Hewlett Packard 8805 B, Andover, USA), an ABC-802 microcomputer (Luxor Datorer AB Motala, Sweden) and a plotter (Hitachi, Tokyo, Japan) as described by Kauppila et al. (1988).

The microtransducer at the top of the catheter measured the bladder pressure and the 5 microtransducers, with a distance of 5 mm between them, measured urethral pressure at different points of the urethra simultaneously. The transducers faced the 3 o'clock position during the measurement. Each transducer registered 300 signals in 1 s. Specific programs for dataprocessing by the computer were developed. The examination began by filling the bladder with physiological saline solution at a rate of 50 ml/min to 300 ml with the patient supine. During this phase the urethrocystometric recordings of bladder and urethral pressures were measured simultaneously at two sites. No abnormalities were found.

While urethral closure function was being examined the patient coughed continuously. The pressure data on 2 to 3 coughs were stored by the computer. Based on our previous findings (Kauppila *et al.*, 1988), we performed this study with the patient standing, and the fourth cough was usually chosen for the detailed evaluation, using specific indicators of urethral closure function: urethral closure pressure (UCP) at rest, UCP at stress and pressure transmission ratio (PTR).

Statistics

Student's paired *t* test (two-tailed) was used in the comparison of pre- and post-operative findings, and the two-tailed *t* test in the comparison of post-operative findings between different groups.

Results

All patients except 1 were satisfied with the result of the operation, the subjective cure rate being 96%. In the patient with subjective disappointment the standing stress test also revealed stress urinary incontinence. Mild voiding difficulties in 4 patients indicated a reduced flow rate. The residual urine volumes were, however, less than 100 ml in each case.

There were no significant differences in the mean (SD) values of UCP at rest between the pre-operative mean of 45·0 cm H_2O (21.6) and the post-operative mean of 50.4 cm H_2O (27.6). Pre-operatively, 20 of 24 patients (83%) had a zero or negative closure pressure at stress (Fig. 1), the negative closure pressure appearing at a bladder pressure of 57 to 213 cm H_2O. In 4 cases the lowest urethral closure pressure at stress varied from 8 to 20 cm H_2O.

The Burch operation increased the UCP at stress in all but 1 patient and the mean UCP at stress was significantly higher post-operatively.

Transmission of the abdominal pressure to the urethra was <100% in 22 of the 24 patients pre-operatively. The operation increased the PTR in all but 1 patient and the mean PTR was significantly higher post-operatively (Fig. 2).

The pre-operative urgency score or grade of incontinence had no significant correlation with the post-operative urodynamic data.

Discussion

We have introduced new urodynamic methods in the pre- and post-operative evaluation of patients. The urodynamic evaluation of urethral closure pressure during the series of 4 coughs lasted for only about 10 s. Processing of the pressure data after investigation was completed in 10 min, resulting in exact recordings of urethral closure pressure at rest and stress, PTR, duration of the negative closure pressure at stress and the minimal bladder pressure needed for the negative closure pressure to

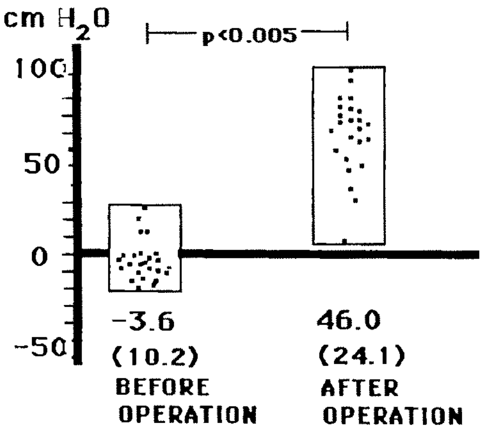

Fig. 1 Urethral closure pressure at stress before and after operation in 24 patients with stress urinary incontinence Measurements were recorded in a standing position during the fourth single cough. Values beneath the columns are mean and SD of individual recordings.

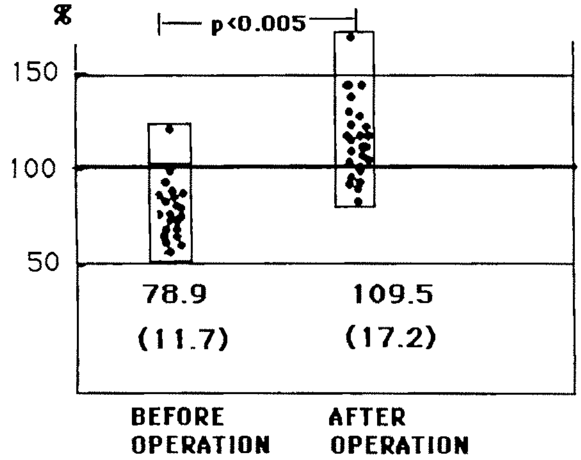

Fig. 2 Pressure transmission ratio (increase in urethral pressure/increase in bladder pressure × 100) before and after operation in 24 patients with stress urinary incontinence Values beneath the columns are mean and SD of recordings.

occur. In addition, the plotter system presented the results graphically. Hence this method compares favourably with the old method with two pressure transducers, one in the urethra and the other in the bladder, commonly used in the urodynamic evaluation of incontinent female patients.

The present method is rapid, giving not only qualitative information but also accurate quantitative data of the severity of incontinence. In the old system for measuring the urethral pressure profile a special motor is needed to move the catheter (urethral transducer) inside the urethra, whereas in the present method the catheter is in the same possition throughout the investigation and the urethral pressure profile can be recorded during one cough.

The fact that the urethral closure pressure at stress was not negative pre-operatively in spite of the visible leakage in 4 cases was due to methodological factors. The stiff catheter does not follow the kinking of the urethra during coughing and sometimes gives erroneous results. This phenomenon is common also with conventional urethrocystometry with a rigid catheter.

Using the modified Burch colposuspension we achieved a cure rate of 96%. The result may be partly due to the short follow-up time of 6 to 9 months. On the other hand, only patients with genuine stress urinary incontinence were treated and the operation was performed each time by an experienced surgeon. The only failure in this series was probably due to technical difficulties when operating on a patient weighing over 100 kg (Tanagho, 1976).

In the present series the operation increased the PTR and the urethral closure pressure at stress was positive. These results confirm the proposal by Hilton (1981) that colpsuspension constructs a novel, mechanical urinary sphincter rather than restores normal sphincter function. We consider that the Burch colposuspension, by elevating the urethrovaginal fascia and fixing it to Cooper's ligaments, creates a stable bottom under the urethra and urethrovesical junction and when the abdominal pressure increases during stress, the urethra is compressed against this fascial plate (Maggio and Raz, 1983; Hertog and Stanton, 1985).

Prerequisites for success in the surgical treatment of stress urinary incontinence are careful urodynamic investigation and the use of surgical techniques which, by correcting anatomical defects in the support of the upper part of urethra and urethrovesical junction, restore pressure transmission conditions in the lower urinary tract. A combination of sophisticated urodynamic methods and surgical skill are therefore needed in the operative treatment of stress urinary incontinence.

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A New Stent for the Treatment of Urethral Strictures
Preliminary Report

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Summary—We describe a new urethral stent which was implanted into 12 patients with urethral strictures. The stent is woven in the form of a tubular mesh from fine stainless steel wire and is self-expanding when released from its small diameter delivery catheter. All patients have been treated successfully, with a good calibre urethra visible on urethrography and direct endoscopy and with improved urine flow rates. The mean follow-up of these patients was 7 months (range 2–13). Urethroscopy demonstrated complete epithelial covering of the implant in 4 to 6 months. Although the follow-up period was short, it seems that this simple technique may offer a lasting treatment for many urethral strictures. A longer follow-up will be necessary to exclude late complications.

The treatment of urethral strictures is still far from ideal. Urethral dilatation is rarely curative, whatever the cause of the stricture, and repeated dilatations are unsatisfactory for the patient and time-consuming for the surgeon. Endoscopic optical urethrotomy was heralded as the definitive treatment for all urethral strictures, but most surgeons would now accept that many strictures recur after this operation. The recently suggested option of repeated self-catheterisation in order to maintain a satisfactory urethral lumen may not be accepted by some patients. One or other of the many varieties of urethroplasty is usually successful in the treatment of traumatic strictures but is less successful for strictures caused by catheters or instruments and those resulting from urethral infection.

We have recently used a new urethral stent ("Wallstent^R": Medinvent SA, Lausanne, Switzerland) for implanting into strictured urethras (Milroy *et al.*, 1988). The stent (Fig. 1) was first developed for endovascular use and has been used successfully for over 2 years in the peripheral arterial system and coronary vessels after transluminal angioplasty (Rousseau *et al.*, 1987; Sigwart *et al.*, 1987).

The urethral stent is woven in the form of a tubular mesh from surgical grade fine stainless steel wire and is produced in various lengths and diameters. When expanded, it is stable though flexible. It is loaded on a small diameter delivery catheter and constrained in its compressed form by a doubled-over plastic membrane, the outer layer of which can be progressively withdrawn in order to allow the stent to expand once it has been located in the region of the previously dilated urethral

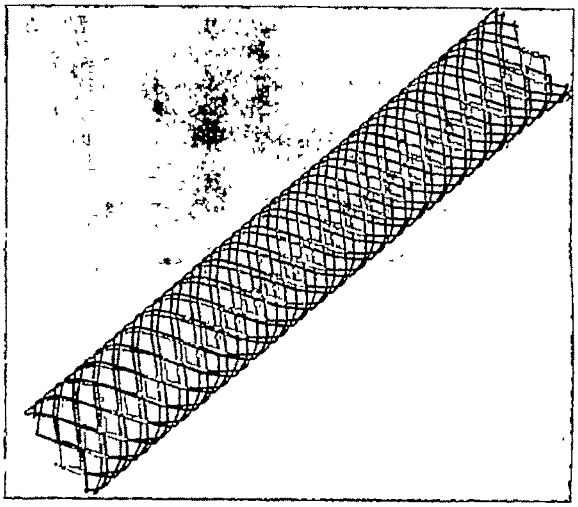

Fig. 1 Urethral stent (Medinvent SA, Lausanne, Switzerland).

Read at the 44th Annual Meeting of the British Association of Urological Surgeons in Buxton, June 1988

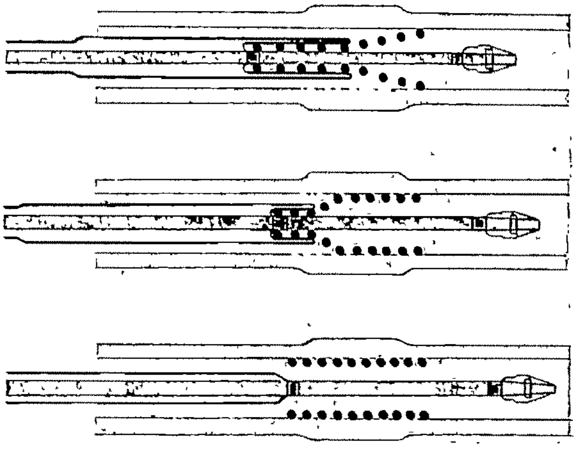

Fig. 2 Diagram of stent release mechanism. Top to bottom; doubled-over ensheathing plastic membrane being retracted and allowing stent to open.

stricture (Fig. 2). Having selected the correct diameter of stent, the elastic properties of the mesh will hold it against the wall of the urethra, preventing migration of the stent and allowing urothelium to grow over the implanted material which becomes incorporated within the wall of the urethra while holding open the strictured area.

Patients and Methods

After experimental studies which demonstrated virtually complete urethral covering of stents inserted into the normal urethras of 4 dogs after 12 months (Milroy *et al.*, 1988), we have now implanted this urethral stent into 12 male patients aged between 31 and 88 years (mean 59). These patients had been treated in the past with at least 2 unsuccessful endoscopic optical urethrotomies and, in 10 patients, multiple urethral dilatations. In each case the patient was awaiting a urethroplasty. The type, duration and site of the strictures are detailed in the Table. Each patient gave informed consent to undergo this new procedure on the understanding that in the event of failure of the stent it would be removed at the time of a subsequent urethroplasty. A total of 17 stents were inserted: 1 stent into each of 9 patients, 3 into 2 patients and 2 into 1 patient.

All patients were treated under general anaesthesia and the urethral stricture was first dilated gently, using filiform and following bougies to 30F. Triradiate optical urethrotomy was necessary in 3 patients but the bleeding associated with this procedure was found to reduce visualisation of the strictured area during subsequent placement of the stent. Following dilatation of the stricture the stents were inserted under radiological control in 2 patients; the remainder were inserted under direct vision, which was found to be a simpler and better technique. The length and diameter of the urethral stent necessary for each patient were assessed from measurements made from the pre-operative urethrogram.

A guide wire was passed alongside a urethroscope and the mesh prosthesis, constrained in its compressed form on the delivery catheter, was then passed over the guide wire. The stent was positioned in the strictured area under direct vision. The delivery catheter was then pressurised with normal saline through a side arm (Fig. 3), to 3 atmospheres, in order to separate the 2 layers of the plastic membrane holding the stent in its compressed state. This allowed the outer layer of the plastic membrane to be withdrawn slowly by movement of the outer sheath of the delivery catheter, permitting the prosthesis to expand. The rate of this expansion could be controlled by adjusting the speed with which the compressing membrane was withdrawn, thereby allowing accurate placement of the expanding urethral stent within the strictured area under direct endoscopic control. Once the membrane had been fully withdrawn and the stent expanded along its full length, the delivery catheter and guide wire were removed.

The delivery catheter was not passed down the inside of the urethroscopy, using the catheterising side arm, in order to avoid damaging the restraining plastic membrance covering the stent. There was also the risk that the stent, as it opened, might get caught within the lumen of the urethroscope.

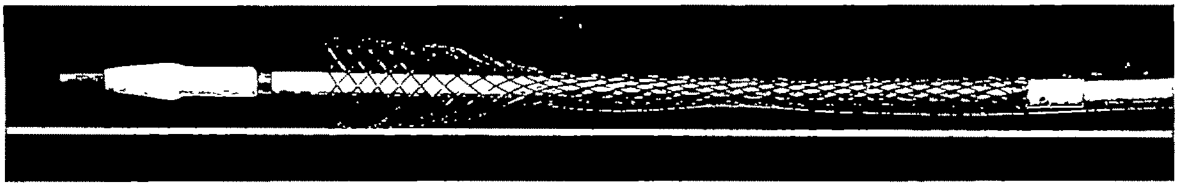

Fig. 3 Close-up view of partially opened stent.

Care was taken to ensure that the internal diameter of the implanted stent was large enough to permit subsequent endoscopic examination and transurethral surgery of the bladder or prostate if necessary. All patients were given prophylactic antibiotic cover for 48 h. No urethral or suprapubic catheter was used and all patients passed urine without difficulty after the procedure.

Results

The patients were reviewed regularly with urine cultures and urine flow rates. Urethrograms and urethroscopies were carried out at intervals of 2, 4, 6 and 12 months.

In all patients the strictures were successfully treated; 5 suffered transient discomfort at the site of the stent for a period of 2 to 3 weeks. One patient had more persistent discomfort, although this had been present in the form of perineal pain before the stent was inserted and the discomfort resolved spontaneously at 7 months. Another patient (T.A.), in whom 2 overlapping stents had failed to cover completely the strictured area, developed a short recurrence at the distal end of the stented urethra after 2 months. This was satisfactorily treated by subsequent dilatation of this area and the insertion of a third overlapping stent. A hyperplastic reaction of the urothelium was noted on a number of occasions at each end of the implanted stent at the time of the earlier endoscopic examination. This reaction had always disappeared by the time the stent was fully covered by epithelium but may result in a little more fibrosis at either end of the stent. Investigations have demonstrated complete epithelial covering of the urethral stent by 4 to 6 months (Fig. 4 and 5) and good calibre urethras with relief of the patient's symptoms, improved urine flow rates and no evidence of stricture recurrence (Fig. 6). One patient (R.B.), whose urethral stricture developed after a cystectomy, complained of inability to ejaculate without regular dilatation of the stricture. Since the insertion of the stent, ejaculation has been normal (Table). Although no patient noted any serious adverse effect on urinary continence, 5 complained of a minor degree of post-micturition dribbling after insertion of the stent. We presume that this is the result of a small volume of urine being held within the lumen of the stent after the completion of micturition. This symptom settled spontaneously in 7 patients in 2 to 3 months, often helped by instructing them to express the posterior urethra after micturition. One patient has more persistent post-micturition dribbling because the stent was inserted a little too close to the distal sphincter mechanism; this is not a serious problem for the patient, who is delighted with the result. No evidence of stent encrustation or infection has been seen. One patient (R.W.), despite pre- and post-implantation urinary infections, has had no prob-

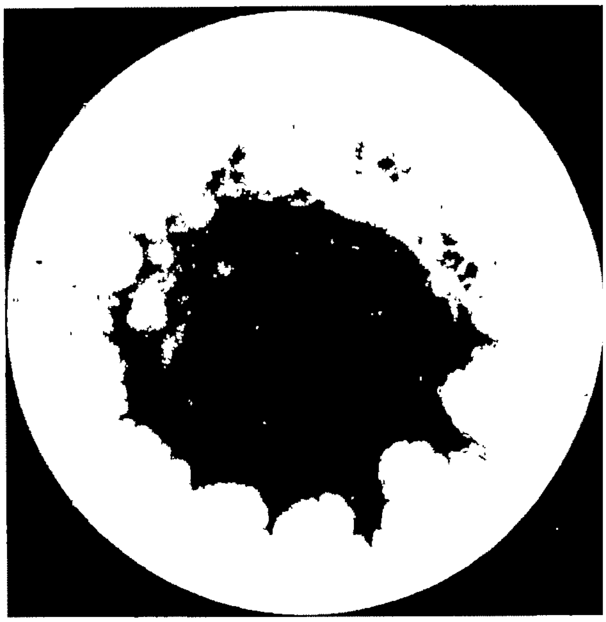

Fig. 4 Endoscopic view of stent covered with hyperplastic urothelium at 4 months.

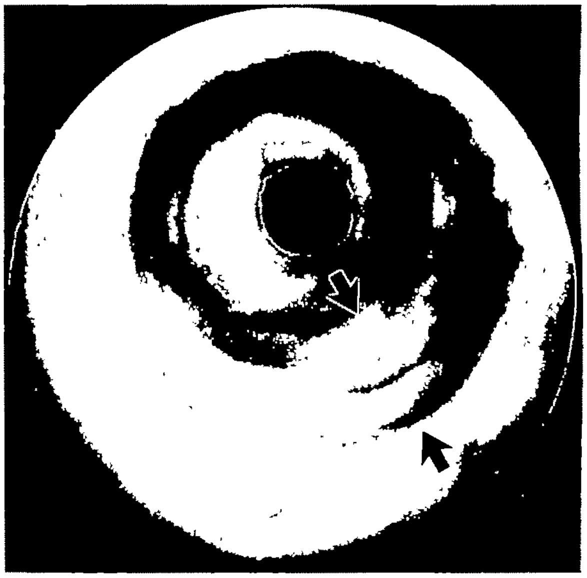

Fig. 5 Endoscopic view 6 months after insertion of stent. Position of stent marked by arrows. Note complete covering by normal epithelium.

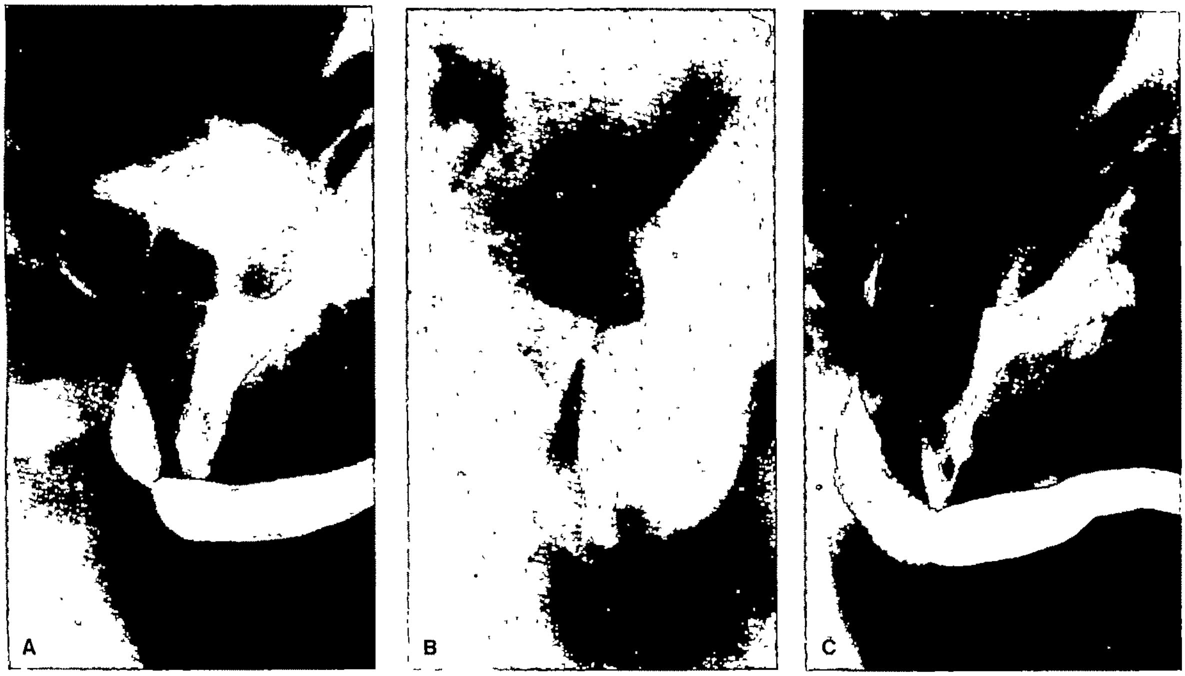

Fig. 6 (A) Urethrogram showing stricture of urethra. (B) Plain film after insertion of stent (C) Urethrogram 4 months after insertion of stent

lems with the stent, which was seen to be completely covered with normal urothelium at 4 months. All patients were advised to avoid sexual intercourse for 1 month after insertion of the stent. After this period no change was found by any patient in his ability to achieve erection or to ejaculate. No difference was noted in the rate of re-epithelialisation or in the final result between infective, traumatic or catheter strictures. No other complications have been experienced. The mean follow-up of these patients was 7 months (range 2–13).

Discussion

This new stent has been used safely in the cardiovascular system for over 2 years with good

Table Details of Patients

Patient	*Age (years)*	*Type of stricture*	*Duration (years)*	*Previous urethrotomies*	*Previous dilatations*	*Site of stricture*	*Peak urine flow rate (ml/s) (all volumes > 200 ml)* Pre-op	Post-op	*Follow-up (months)*
N.H	60	Catheter	3	4	0	Bulb	8.8	22.7	13
F.J	67	Post-TUR	7	2	34	Bulb	6.2	23 7	13
T.A	54	Infective	23	2	30	Bulb	10.1	29 6	9
J M	77	Traumatic	8	2	3	Bulb	6.9	13 0	9
A G.	44	Instrument + infective	36	2	6	Bulb + Meatus	9.2	18 6	9
R.W	78	Post-TUR	2	2	3	Bulb	6 9	16.2	6
M Z	33	Infective	3	2	2	Bulb	10 8	34 6	6
R B	54	Post-cystectomy	7	4	2	Membranous	Obstructed ejaculation	Normal ejaculation	6
H K	62	Catheter	2	2	1	Bulb	2 5	23 6	4
P.B	31	Infective	10	2	5	Bulb	8 8	28.4	4
J.B.	67	Post-TUR	10	8	33	Bulb	9 2	23 5	3
I L.	88	Post-TUR	15	6	0	Bulb	5 3	17.0	2

results and few complications (Rousseau *et al.*, 1987; Sigwart *et al.*, 1987). The transitional cell urothelium is remarkable for its ability to cover defects rapidly and the frequent recurrence of strictures in the proximal urethra makes it an ideal area to use this form of implantable stent which can be covered by urothelium on its inner surface and become incorporated within the wall of the urethra while holding open the strictured area. This avoids the well recognised failures of intraluminal urinary stents, which are associated with calcific encrustations and infection. The technique of insertion is simple, although great care must be taken in selecting the correct size of stent and in its accurate placement within the strictured area. As the stent opens it shortens and this can easily lead to incomplete covering of the dilated stricture and a partial recurrence at one end of the stent. We have been unable either to reposition or to remove a stent once it had opened within the urethra, necessitating the immediate insertion of a second overlapping stent in 2 patients and the later insertion of another stent in these 2 and a third patient. However, a new and less complex device has been designed for inserting the stents and it can also be used to remove the stents endoscopically. This should ease the problem of accurate placement and reduce the need for additional stents.

Urethral strictures are notorious for the frequency with which they recur after apparently successful treatment. The follow-up of these patients is short and they will need to be kept under review for 5 to 10 years before they can be described as cured and before one can be sure that no long-term problems result from the implantation of this stent. This appears to be the first reported treatment for urethral strictures which mechanically holds open the area of fibrosis, although remaining flexible, and allows normal epithelialisation to occur within the lumen.

The use of this stent has been deliberately limited to short strictures in the bulb of the urethra which had failed to respond to other treatments. If the long-term results are satisfactory, it will be possible to treat more complex strictures and those which occur in other areas of the urethra.

This technique offers the possibility of replacing repeated dilatations, urethrotomies and the many different varieties of difficult urethroplasty operations with a simple and effective treatment for many urethral strictures.

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Urethral Strictures following Transurethral Resection of the Prostate. The Role of the Catheter

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Summary—Urethral stricture is the most common late complication of transurethral prostatectomy (TURP). The cause is unknown. A prospective, randomised study was undertaken to investigate the role of the transurethral catheter in stricture formation. A total of 205 patients subjected to TURP were studied. Following resection, they were randomly divided into 2 groups: those drained by a transurethral siliconised latex catheter and those drained by a suprapubic siliconised latex catheter. At follow-up, 6 to 24 months later, 17% of the patients in the transurethral group had developed urethral stricture; the corresponding figure in the suprapubic group was 4%. As a consequence of the higher incidence of stricture in the transurethrally drained group, more patients in that group were dissatisfied with the results of the operation. It was concluded that the post-operative transurethral catheter was an important factor in stricture formation following TURP and that transurethral drainage with a siliconised latex catheter resulted in a higher incidence of stricture. This led to a greater number of patients being dissatisfied with the results of the operation, but the catheter did not affect the results in any other way.

Transurethral resection of the prostate is a widespread operation for symptomatic prostatic obstruction. The low complication and mortality rates have contributed to its frequent use. However, the formation of urethral strictures is the most common late complication. The incidence varies between 4% (Warres, 1958) and 29% (Holtgreve and Folk, 1964) and the cause is not known. Urethral instrumentation during the operative procedure or the presence of a transurethral catheter in the post-operative period and/or a combination of these factors are the most plausible causes.

Previous studies have shown no relationship between post-operative stricture formation on the one hand and urinary tract infection, length of resection time, weight of prostate resected, duration of post-operative catheterisation or histological diagnosis of the resected tissue (Lentz *et al.*, 1977, Bailey and Shearer, 1979) on the other.

It has been reported that TURP via perineal urethrotomy (Bissada, 1977), pre-operative dilatation of the urethra (Lentz *et al.*, 1977) and Otis internal urethrotomy (Emmett *et al.*, 1963; Bailey and Shearer, 1979) can lower the incidence of stricture formation, but no conclusions can be drawn from these reports concerning the aetiology of the condition.

We performed a prospective, randomised study to investigate the role of the post-operative transurethral catheter in the formation of urethral strictures following TURP.

Patients and Methods

After completion of the resection, the patients were randomly divided into two groups, one with a transurethral catheter and the other with a suprapubic catheter. A trocar of sufficient diameter (32F) was constructed to permit the passage of a suprapubic catheter into the bladder.

Of the 205 patients studied, 104 were in the suprapubic and 101 in the transurethral group. All patients subjected to TURP were included, except for those with a history of urethral stricture or a urethral stricture demonstrated at the preliminary urethrocystoscopy; thus 24 were excluded from the

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suprapubic group and 13 from the transurethral group. Two patients were excluded from each group because of a history of urethral stricture and 8 died before follow-up of causes unrelated to surgery. Six patients in the suprapubic group and 3 in the transurethral group were supplied with a urethral catheter during treatment of a disease not related to the prostate before follow-up; 8 patients in the suprapubic group had local complications requiring a post-operative per-urethral catheter. Thus 88 patients in the transurethral group and 81 in the suprapubic group were available for study.

TURP was performed for the usual indications under general or epidural anaesthesia. The operation area was cleaned with 1 mg/ml chlorhexidine and the urethra disinfected with 2% prilocain hydrochloride and chlorhexidine lubricating jelly (Citanest). Resection was performed using the 24F Storz resectoscope; 3% glycine solution was used as irrigation fluid during surgery. The resection was performed with a suprapubic trocar as continuous drainage. Following resection, this was replaced by a 22F self-retaining, 3-way siliconised catheter in the suprapubic group. In the transurethral group, the same type of catheter was passed *per urethram* and left *in situ*. We have used this type of catheter routinely for several years. Both groups had continuous irrigation of the urinary bladder until the urine had cleared. The suprapubic incision was closed with a stitch.

Follow-up examination was performed on an out-patient basis after 6 to 24 months. Patients were asked if they were satisfied with the urinary flow. Those with symptoms suggestive of stricture and/or maximal urinary flow <15 ml/s were subjected to urethroscopy. Stenosis of the urethra with a circumference <19 mm was defined as a stricture. The chi-squared test was used in the statistical calculations.

Results

Of the 88 patients in the transurethral group, 33 had symptoms suggestive of stricture and/or a maximal urinary flow <15 ml/s and were followed up with urethroscopy. Of the 80 patients in the suprapubic group, 21 required urethroscopy. In the transurethral group, 15 patients (17%) had developed a stricture; in the suprapubic group the corresponding figure was 3 patients (4%). This difference was statistically significant ($P<0.01$) (Table 1). The sites of the stricture are shown in Table 2. Seven patients in the transurethral group and 2 in the suprapubic group with a documented urethral stricture had no symptoms of obstruction but a low maximal urinary flow.

Table 1 Incidence of Stricture Formation

	No. of patients	*No. of strictures*	%
Transurethral group	88	15	17
Suprapubic group	80	3	4*

* $P<0.01$.

Table 2 Site of Stricture

	Transurethral group	*Suprapubic group*
	No.	*No.*
External meatus	4	
Navicular fossa	4	1
Peno-scrotal	4	
Bladder neck	3	2

At follow-up, 16 patients (18%) in the transurethral group were dissatisfied with the results of the operation (Table 3). In 8 patients this could be related to a stricture, in 7 to residual adenoma and in 1 patient no apparent cause could be identified. In the suprapubic group, 6 patients (7.5%) were dissatisfied. This number was significantly lower than in the transurethral group ($P<0.05$). The reason for dissatisfaction was stricture in 1 patient ($P<0.05$) and residual ademona in 4. In 1 patient no apparent cause could be found.

Both groups were analysed with respect to other pre-, per- or post-operative factors possibly affecting urethral stricture formation (Table 4). The groups did not differ significantly with regard to age, histological diagnosis, pre-operative cystoscopy, pre- and post-operative maximum urinary flow rate, indwelling catheters prior to operation, length of resection time, weight of prostate resected, post-operative catheter time or time in hospital. There

Table 3 Causes of Dissatisfaction with Results of TURP

	Transurethral group ($n=88$)	*Suprapubic group ($n=80$)*
Stricture	8	1*
Residual adenoma	7	4
No cause found	1	1
Total	16	6*

* $P<0.05$.

Table 4 Data on Patients Subjected to TURP

	Transurethral group (n = 88)	*Suprapubic group (n = 80)*
Mean age	72 ± 7	71 ± 7
Prostatic hyperplasia	80%	76%
Prostatic cancer	20%	24%
Prostatitis	10%	7%
Pre-operative cystoscopy	48%	53%
Indwelling catheter prior to operation	53%	49%
Pre-operative maximum urinary flow (ml)	8 ± 3	8 ± 3
Post-operative maximum urinary flow (ml)	17 ± 8	20 ± 10
Length of resection time (min)	47 ± 15	49 ± 20
Weight of prostate resected (g)	17 ± 10	20 ± 13
Post-operative catheter time (days)	3.3 ± 2	4.7 ± 2
Time in hospital (days)	6.5 ± 3	7.5 ± 3

was no mortality and the complication rate did not differ between the groups.

Discussion

A stricture incidence of 17% in the transurethral group is similar to the incidence reported in other series (Kristensen *et al.*, 1985; Meyhoff, 1987). The difference in incidence between the 2 groups in our study shows the influence of the urethral catheter in the formation of strictures following TURP. Thus the urethral catheter plays a more important role than other factors during the operative procedure. Three strictures in the transurethral group and 2 in the suprapubic group were found in the bladder neck. The main difference in incidence between the groups was in the anterior urethra and it is possible that strictures in the bladder neck are not related to indwelling catheters.

Lentz *et al.* (1977) presented a hypothesis concerning the aetiology of stricture formation following TURP, stating that the initial damage is a mucosal lesion which leads to a leakage of urine and causes inflammation and scar formation.

The present study indicates the possibility of the catheter acting as a "foreign body" in the mucosal lesion, keeping the wound wide open; this initiates and sustains an infection that ultimately results in scar formation and a urethral stricture. However, other factors may also contribute. The catheter used in this study was made of a latex core covered with a film of silicon oil. It is well known that this coating is not stable in a tissue environment and melts away in a few hours, leaving a surface of latex which may be toxic to the urethral mucosa (Talja, 1986). Whether or not this is a major mechanism in stricture formation following TURP can be evaluated only by testing catheters of different materials in a similar prospective, randomised study. Such a study is now in progress.

Regardless of the mechanism of stricture formation following TURP, this study shows that transurethral catheters increase the incidence of urethral strictures. It is noteworthy that 7 of 15 patients in the transurethral group had urethral strictures that produced no symptoms other than a low maximal urinary flow. The patients were followed up after 6 to 24 months. It is possible that some of these symptom-free patients will have obstructive symptoms related to the stricture in the future.

In the suprapubic group, 93% of the patients were satisfied with the results of the operation. This compares favourably with the findings in other series (Chilton *et al.*, 1978; Abrams *et al.*, 1979; Meyhoff, 1987).

On the basis of this study, however, suprapubic drainage cannot generally be recommended for the purpose of lowering the incidence of stricture formation following TURP, since the high incidence of strictures following the use of siliconised latex catheters does not necessarily hold true for catheters made from other materials.

It is concluded that the post-operative transurethral catheter plays an important role in stricture formation following TURP. Whether this is related to a mechanical or a chemical mechanism has not been determined. As a consequence of the higher stricture incidence in the transurethrally drained group, more patients were dissatisfied with the results of the operation.

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One-stage Repair of Hypospadias Using Split Preputial Flaps (Harris)

The First 100 Patients Treated

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Summary—An analysis is presented of the outcome in the first 100 patients treated by a new technique for the repair of hypospadias and congenital short urethra associated with chordee. Further reconstructive surgery was required in 24 patients. The effect of the position of the meatus, the length of the reconstructed urethra and the method of urinary drainage are analysed. Minor complications are described. A significantly higher complication rate was associated with a per-urethral than with a suprapubic catheter; 5 of the 38 patients in whom a suprapubic catheter was used developed complications requiring reconstructive surgery. Possible causes of the complications are discussed and the results compared with those of other methods. It was concluded that this is a satisfactory method of repair for hypospadias associated with chordee.

As an extension of Asopa's original concept of using the internal skin of the prepuce as a transverse island flap for a neo-urethral tube in the one-stage repair of hypospadias (Asopa *et al.*, 1971), Duckett (1980) and Harris (1984) discovered independently that the external preputial skin can be dissected from the island flap of internal skin with the preservation of an adequate blood supply to both layers of skin. The advantage of doing so lies in the ability to remove surplus external preputial skin at the end of the operation to improve the normality of appearance which is so important for the patient's later self-confidence. The essential differences between Duckett's operation and the one described in this report are the operative methods for splitting the prepuce into its two layers and the formation of the external meatus. In Duckett's technique the prepuce is split after its internal skin has been tubed for the neo-urethra and the meatus is created by tunnelling the neo-urethra through the glans penis.

A detailed analysis is presented of the results of the first 100 patients treated by the Harris method between July 1976 and March 1985. The study includes 50 patients whose results were reported when the method was first described (Harris, 1984).

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The Operation (Figs 1–4)

A sub-coronal circumscribing incision which runs distal to the urethral opening transects the chordee, which is dissected proximally and distally off the corpora cavernosa. The opening in the urethral stump which is surrounded by corpus spongiosum is enlarged into an oval. A V-shaped incision is made on either side of the navicular fossa and triple glans flaps raised (Devine and Horton, 1961).

The whole prepuce is brought round to lie with its horizontal axis alongside the shaft of the penis on the right by making an oblique back cut into its left dorso-lateral surface which coincides with the underlying sub-coronal incision. The transposed prepuce is pinned to a tile cut from a sheet of silicone rubber.

The prepuce is incised around its distal margin and the internal skin is dissected from the external skin along an avascular plane of fibrous tissue which separates the vascular territories of the two layers of preputial skin. The islanded internal skin flap is tailored to the size and shape required for a neo-urethra; its calibre matches that of the normal urethra. It is tubed and anastomosed proximally to the urethra and distally to the central glans flap. The lateral glans flaps are brought together over

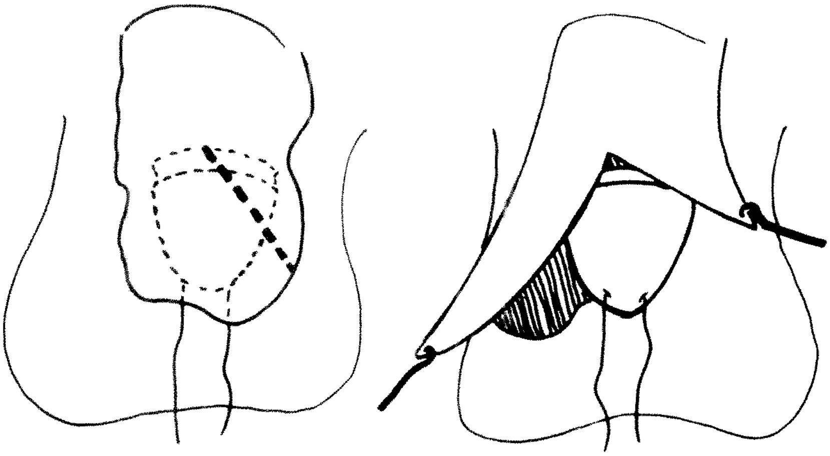

Fig. 1 Dorsal back cut through external skin of the prepuce to allow the whole prepuce to rotate through 90° so that its horizontal axis can lie parallel with the shaft of the penis. (Reproduced from the *British Journal of Plastic Surgery* (1984), **37**, 108–116.)

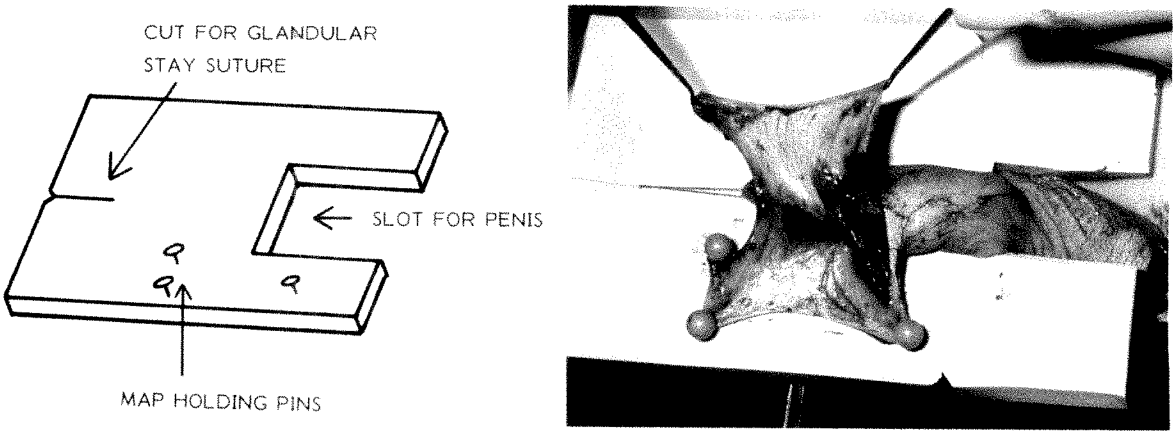

Fig. 2 Diagram of tile cut from ¼" thick silicone rubber sheet and photograph of penis showing external preputial flap pinned to the tile with internal preputial flap distracted with skin hooks after their dissection. Note separate leashes of blood vessels for each flap.

the distal end of the neo-urethra. The external skin flap is trimmed to fit the defect of ventral skin and sutured into place. The penis is wrapped in a four-tailed dressing cut from Reston self-adhering foam pad (3M Company) and compressed with a gauze bandage.

Three different methods of urinary diversion have been used. In the first 42 patients, urine was diverted for 10 days post-operatively via a Foley catheter which was introduced through a perineal urethrostomy (PU). In the next 20 patients the bladder was drained *per urethram* via a fine red rubber catheter (PUC) which was introduced at the end of the operation; the catheter was secured to the penile dressing and removed on the fourth post-operative day. In the last 38 patients the urine was diverted through a 10F suprapubic Argyle catheter (SPC) which was introduced into a distended bladder through a stab wound created with a number 11 scalpel blade; the catheter was removed on or about the tenth post-operative day after a satisfactory trial of micturition.

All but 6 of the operations were performed by one surgeon (D.L.H.).

Patients and Methods

Two of the 100 patients were treated for congenital short urethra. The remainder had hypospadias with chordee. Following radical excision of chordee the

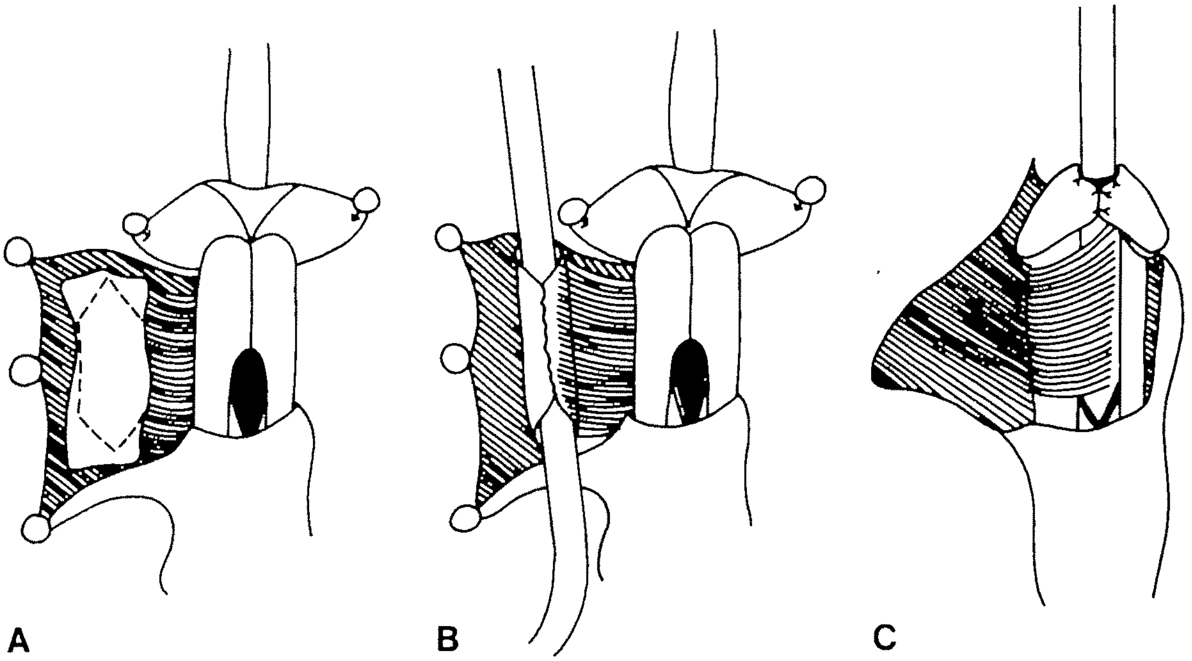

Fig. 3 (A) Marking of internal preputial flap measured for neo-urethra Note oval opening of urethral stump and radical mobilisation of glans from corpora cavernosa The central glans flap is turned down ready for anastomosis to the neo-urethral flap The lateral glans flaps are pinned to the tile (B) The tailored internal skin flap tubed around a bougie or silastic tube which fits the urethra (C) After anastomosis of the neo-urethra to the urethral stump and the central glans flap The lateral glans flaps are sutured together over the glanular part of the neo-urethra in which lies a bougie to prevent overtight closure. (Reproduced from the *British Journal of Plastic Surgery* (1984), 37, 108–116)

urethral orifice was placed in the distal half of the penis in 76 patients, in the proximal half in 19 and in the perineum in 5. Most patients were in their third or fourth year at the time of operation. There was 1 adult (Table 1).

During the series an additional 45 patients were treated for hypospadias without chordee either by Matthieu's "flip-flap" (Devine and Horton, 1961) or by cosmetic circumcision. In 2 other patients with perineal hypospadias, the prepuce was too small for the method of split preputial flaps to be used; they were treated by a two-stage procedure (Van der Meulen, 1971). The results in these patients are not included in this report.

Data for analysis were collected from a review of the patients' hospital records. Most patients without complications were reviewed 3 and 15 months postoperatively and then discharged. Some patients treated early in the series were reviewed for up to 3 years. With increasing confidence in the success of the operation such long-term follow-up was considered unnecessary for subsequent patients. All complications requiring further reconstructive surgery were apparent within 3 months of the original operation. Of 13 patients who have been followed

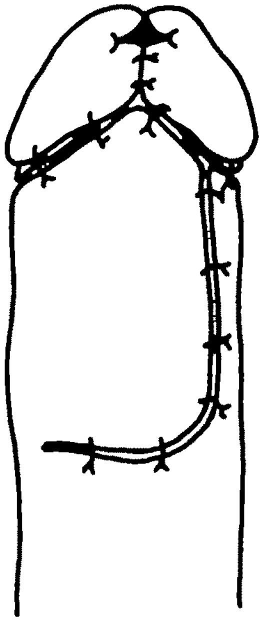

Fig. 4 The suture line of the external preputial flap after it has been rotated 45° from its original position, folded over the ventral surface of the penis and trimmed to fit the deficit of skin (Reproduced from the *British Journal of Plastic Surgery* (1984), 37, 108–116.)

Table 1 Age at Operation

Age (years)	*No. of patients*	*No. requiring further reconstructive operations*	*(%)*
2	6	1	17
3	55	15	27
4	25	5	20
5–11	13	3	23
21	1	0	0

Table 2 Patients Requiring Further Reconstructive Operations

Complication	*Urinary drainage*	*No. of further reconstructive operations*
Congenital short urethra (2)		
A Fistula (proximal)	PU	2
B Fistula (proximal)	PU	1
Distal hypospadias (74)		
C Stenosis (proximal)	PU	2
D Ballooning	PU	1
E Stenosis (distal)	PU	1
F Fistula (proximal)	PU	1
G Stenosis (meatal)	PU	2
H Stenosis (proximal)	PUC	1
I Fistula (proximal) Necrosis of external skin flap	PUC	2
J Fistula (proximal)	PUC	3
K Stenosis (proximal)	PUC	2
L Stenosis (proximal) Stenosis (meatal)	PUC	3
M Fistula (distal)	PUC	2
N Fistula (distal)	SPC	1
O Fistula (distal) Ballooning	SPC	1
P Fistula (proximal)	SPC	1
Q Fistula (proximal)	SPC	1
R Fistula (proximal)	SPC	1
Proximal hypospadias (19)		
S Stenosis (meatal) Ballooning	PU	2
T Necrosis of external skin flap	PU	2
U Fistula (proximal)	PUC	1
V Stenosis (proximal)	PUC	2
Perineal (5)		
W Fistula (proximal)	PU	5
X Stenosis (proximal) Occlusion (distal anastomosis) Ballooning	PUC	3

up for less than a year with no apparent complications, all were satisfactory 3 months after the operation; 6 lived abroad or moved out of the area and 1 failed to attend for review.

Results

One child died a year after the operation from a cause unrelated to his hypospadias.

The patients were divided into 3 groups; those with no complications at all, those with minor transient complications and those with significant complications which required further reconstructive surgery.

Patients requiring further reconstructive surgery (Table 2)

Thirteen patients developed fistulae, 10 at the level of the proximal anastomosis and 3 at the level of the glans penis. The probable causes of fistula formation were identified in 7 patients; wound infections caused by *β-haemolytic streptococcus*, probably entering via the perineal urethrostomy (patients B and W); faecal soiling and recurrent urinary tract infections (patients F); disruption of the proximal anastomosis following removal of the PUC for retention 7 days post-operatively (patient U); early removal of the SPC (patient N); dehiscence of the suture line of the external skin flaps (patients I and O).

Nine patients developed stenoses, 6 at the level of the proximal anastomosis and 5 at the distal anastomosis. Of the proximal stenoses, 5 occurred in patients with per-urethral catheters. Infection was thought to have contributed in 3 patients: with *Escherichia coli* (patient C, who had a perineal urethrostomy), with *bacteroides* (patient X) and with "mixed infection" (patient L). Both of the latter patients had per-urethral catheters and both also developed meatal stenosis.

In patient G, early retention necessitated a change of the perineal catheter. Patient E's catheter became dislodged within 24 h of surgery and at subsequent operation the distal anastomosis was found to be disrupted.

The proximal stenoses were treated by a two-stage urethroplasty (Johanson, 1953).

Partial necrosis of the external skin flap occurred in 2 patients. In both cases, the necrotic portions were excised and the lumen of the underlying urethra was exteriorised. The consequent fistula was closed once post-operative induration had resolved. This approach was also used for the treatment of a combined proximal stenosis with fistula. Patient J required recruitment of further tubed ventral penile skin to extend the neo-urethra. Three patients required reduction of the calibre of the neo-urethra to correct ballooning (discussed below).

Table 3 Length of Reconstructed Urethra (91 recorded)

	No of patients	*No. requiring further reconstructive operations*	*(%)*
<3 cm	83	18	22
≥3 cm	8	4	50

All of the flaps of internal preputial skin survived; the median length was 2.2 cm (range 1.2–6) (Table 3).

Minor complications

Seven patients had a transient fistulous leak, usually from the region of the proximal anastomosis, which closed spontaneously during the first post-operative month. Some patients had a weak stream initially which strengthened to normal with resolution of post-operative oedema and induration. The patency of the urethra was confirmed in 2 of these patients by examination under anaesthesia. Ballooning of the neo-urethra which did not require correction was noted in 2 patients.

Five patients had dysuria or urinary tract infection which resolved without sequelae following appropriate treatment. Bleeding from the suture lines or haematuria occurred in 3 patients. One child suffered nightmares about men in green suits.

In 10 children who did not require further reconstructive surgery at least one further general anaesthetic was required for reinsertion of the catheter (2), re-application of a dressing (1), examination of the urethra (3), urethral dilatation (1), arrest of haemorrhage 8 days post-operatively (1) and trimming of the dog-ear of the external skin flap (4).

Discussion

The concept of splitting the prepuce to produce two independently vascularised flaps has significantly advanced the surgical treatment of hypospadias and related anomalies. Each flap can be adjusted in size and shape to reconstruct, precisely, the neo-urethra and the deficit of ventral skin without jeopardising the circulation of the other. In particular, excess skin covering the shaft of the penis can be safely excised at the time of the one-stage hypospadias reconstruction. This is not true for techniques of hypospadias repair which use an island flap of preputial skin that remains attached to the rest of the prepuce (Hodgson, 1970; Toksu, 1970; Asopa *et al.*, 1971).

The results of the Harris operation are similar to those of the Duckett operation. Of the 33 patients treated by D.L.H. personally, using a suprapubic catheter, 4 required further reconstructive surgery (12%). Duckett (1984) reported his complication rate at between 12 and 14%; the results of 101 Duckett operations done by others revealed an average complication rate of 26%: fistulae (13%) and stenoses (13%) (de Sy *et al.*, 1981; Parsons and Abercrombie, 1982; Monfort *et al.*, 1983; Bondonny *et al.*, 1984). Monfort *et al.* (1983) commented that, with increasing experience, the complication rate fell from 25 to 10%. In all of these reports the viability of the island flaps used to reconstruct the neo-urethral tube was consistently good: partial necrosis of the skin flaps used for reconstruction of the ventral skin defect occurred twice in this series and twice in that reported by Duckett (1980).

If the concept is good, how can the incidence of post-operative complications be reduced? A number of lessons have learnt whilst treating the patients in this series.

The route of urinary drainage (Table 4)

The incidence of complications was least among patients with suprapubic catheters, intermediate among those with perineal urethrostomies and highest among those with per-urethral catheters. Using a chi-squared test, the difference between the complication rate in patients drained suprapubically and those drained per-urethrally was statistically significant. ($P < 0.02$).

Perineal urethrostomies provide a portal of entry for pathogenic bacteria (Woodard, 1981), predisposing to wound breakdown and fistula formation. Particularly in children, the balloon of a Foley

Table 4 Method of Urinary Drainage

	No of patients	*Fistula*	*Stenosis*	*Other*	*Total**	*%*
Perineal urethrostomy	42	4	4	3	10	24
Per-urethral catheter	20	4	5	2	9	45
Suprapubic catheter	38	5	0	1	5	13
Total	100	13	9	6	24	24

*Some patients had more than one complication catheter is liable to cause strangury and tenesmus through pressure on the bladder neck and rectum and it does not reliably prevent urine leaking down the urethra with the consequent risk of fistula formation (Allen, 1981). It was because of these disadvantages that a per-urethral route of drainage was used.

It is postulated that the higher rate of complications (proximal stenosis in particular) which occurred in patients treated with per-urethral drainage was caused by disruption of the anastomosis either by the introduction of the catheter or during its withdrawal on the fourth post-operative day. The red rubber may also have acted as an irritant (Moore, 1958). There was a greater tendency for patients with urethral stents or catheters to have crusting around the external meatus.

The evidence from this series strongly supports the recommendations of others (Duckett, 1980; Kaplan, 1981; Woodard, 1981) that suprapubic drainage is the route of choice: it is easy and safe to establish, it is comfortable for the child, there is minimum risk of bacterial infection and it allows for trial micturition once the penis appears to be healed.

The proximal anastomosis

The majority of complications occurred at the site of the proximal anastomosis. Bondonny *et al.* (1984) emphasised the need to resect all of the urethral mucosa which is not surrounded by corpus spongiosum. Adherence to this dictum is strongly advised. Failure to do so in 1 patient in this series was the certain cause of subsequent stenosis.

An oblique junction between the urethral stump and the neo-urethra is least likely to cause narrowing of the lumen as the junctional scar contracts. However, even minor slippage between the two oval ends will create immediate narrowing of the urethral lumen at the site of the anastomosis. Breakdown of the anastomosis was observed in 1 patient when its site was explored and resutured. Transient fistulous leaks and extravasation of urine in 6 patients following resumption of micturition provided further evidence that separation of wound edges at the site of the proximal anastomosis might be the principal cause of complications at this site. The anastomosis was fashioned with interrupted 6/0 plain catgut sutures with the knots tied intraluminally; 6/0 chromic catgut is now used.

The external meatus

The formation of an external meatus using the triple glans flap technique of Devine and Horton (1961) has given consistently good results. The meatus looks normal, spraying is rarely a long-term post-operative problem, and meatal stenosis requiring either dilation or surgical treatment occurred in only 6 patients. There is no need to maintain the patency of the external meatus by routine post-operative dilatation, as is advocated for the Duckett operation (Duckett, 1980).

Three points of technique are worthy of attention. It is essential to suture the apex of the neo-urethra securely to the junctions between the central and the lateral glans flaps; if the neo-urethra slips back off the central glans flap a meatal stricture will develop. Fibrous tissue deep to the navicular fossa should be excised to allow the central glans flap to fold in half vertically. A bougie of the urethra's calibre should lie in the neo-urethra when closing the lateral glans flaps over its distal end in order to prevent overtight closure.

The neo-urethral tube

The prepuce is split into two flaps prior to tailoring and tubing of the island flap of internal skin for the neo-urethra. Splitting the prepuce along the plane of avascular fibrous tissue which intervenes between the vascular plexuses supplying the two layers of skin can be done with ease and accuracy by pinning the external skin to a silicone rubber tile and progressively distracting the internal skin as it is mobilised (Harris, 1984). The vessels supplying the two flaps are easily seen; the larger ones usually belong to the external skin flap. None needs to be divided. Both cases which were complicated by partial necrosis of the external skin flap were treated early in the series, when there was a tendency to keep the larger vessels in the pedicle of the internal skin flap. The neo-urethra should always be designed from the end of the internal skin flap which lies distally when the prepuce is rotated (*i.e.* the lefthand edge of the prepuce if it is rotated to the right). A torsional deformity may result if the neo-urethra is designed from the proximal end of this flap.

Since ballooning of the neo-urethra became apparent in 5 patients treated early in the series, particular attention has been paid to adjusting the width of the internal skin flap so that it fits exactly the circumference of a urethral sound selected to match the calibre of the child's natural urethra (usually 12F). If anything, the calibre of the neo-urethra should be slightly narrower. Failure to match the calibre of the neo-urethra with that of the natural urethra will increase turbulence, raise intraluminal pressure and risk fistula formation

(Townsend, 1975). Ballooning of the neo-urethra will also promote the risk of pooling of seminal fluid later in life.

Reconstruction of the ventral skin defect

The choice is between transferring the external preputial skin to the ventral aspect of the penis in two halves by the Byar technique (Duckett operation) and transferring it as a single flap by the van der Meulen technique (Harris operation). It is argued that the latter is preferable: the suture line of skin closure lies well away from that of the neo-urethra and there is a single dog ear which can be safely trimmed. The closure of Byar flaps overlies or crosses the neo-urethra, there are more scars and there are two dog ears, the trimming of which can jeopardise the circulation to the tips of the flaps.

The results of this series add to the accumulating evidence that splitting the prepuce into two flaps for the reconstruction of the urethra and the deficit of ventral skin in hypospadias is both reliable and effective, at least in the short term. The concept has also been applied successfully to the reconstruction of stenosed segments of the penile urethra which have failed to respond to endoscopic treatment. To minimise the incidence of complications requiring further reconstructive surgery the following points are made:

1. The bladder should be drained suprapubically.
2. The neo-urethra should be fashioned accurately to fit the deficient length and calibre of the natural urethra.
3. Meticulous attention must be paid to the suturing of both the proximal anastomosis and the flap at the reconstructed external meatus.

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Serum Lactate Dehydrogenase and Human Choriogonadotrophin in Seminoma

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Summary—The clinical significance of serum lactate dehydrogenase (LDH) and serum human choriogonadotrophin (HCG) as tumour markers was assessed in 105 patients with pure seminoma from whom 981 blood samples were analysed. The specificity of elevated HCG and LDH was 100 and 93% respectively. The comparable sensitivity was 32 and 47%. Serum LDH could not discriminate between patients with clinical stage I seminoma, prior to orchiectomy, and those with benign testicular lesions. In patients with advanced metastatic seminoma subjected to orchiectomy, serum LDH was increased in 82%, but elevated HCG was found in only 40%. After cisplatin-based chemotherapy, falsely elevated LDH was observed in 7 of 37 tumour-free patients, but HCG was normal in all patients with no evidence of disease. Six patients with residual tumour after chemotherapy had normal LDH and 4 of them had elevated HCG; 70% of the relapses in seminoma patients were associated with increased LDH (64%) and/or HCG (48%). In seminoma patients with comparable disease extension, elevated HCG seemed to be correlated with a high risk of relapse. Patients with normal pre-treatment LDH had a lower relapse-free survival rate than patients with elevated LDH. HCG is a highly specific tumour marker in seminoma with a rather low sensitivity. HCG is particularly useful for the primary diagnosis in patients with testicular lesions and during monitoring of chemotherapy in seminoma patients. LDH is less specific than HCG. Both markers should be analysed during follow-up of seminoma patients, since 70% of relapses are associated with an increase in one or both markers. Elevated pre-treatment HCG, but not elevated LDH, seems to indicate an increased risk of relapse in patients with seminoma.

The treatment of testicular cancer has improved dramatically during recent years (Fosså *et al.*, 1988) and part of this improvement is due to efficient tumour monitoring with reliable tumour markers. This is particularly true for non-seminoma, where alpha-feto protein (AFP) and HCG are useful. In seminoma patients, however, monitoring of the disease is hampered by the lack of reliable markers.

It is stated that HCG is the best serum tumour marker available for seminoma today (Lange *et al.*, 1980; Morgan *et al.*, 1982; Nørgaard-Pedersen *et al.*, 1984; Ford *et al.*, 1985; Paus *et al.*, 1987). However, the value is critically dependent on the HCG assay used because many patients produce HCG immunoreactive material which represents not-intact HCG (Paus *et al.*, 1987).

Placental alkaline phosphatase (PLAP) is of some value, but its serum levels are dependent on the smoking habit of the patients (Lange *et al.*, 1982; Jeppsson *et al.*, 1983). This problem is reduced if monoclonal antibodies are used which specifically react with PLAP-like enzymes. The normal testis also produces PLAP-like enzymes and this impairs the ability to find the true positive PLAP producers except with the most specific assay (Millan and Stigbrand, 1983).

LDH, especially LDH1, has been described as a good marker for seminoma (Lippert and Javadpour, 1981; von Eyben *et al.*, 1983; Taylor *et al.*, 1986). LDH is a glycolytic enzyme found in all living cells. It is measurable in the blood of healthy individuals

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and its activity in serum is increased in a number of malignant and non-malignant diseases (Cohen *et al.*, 1965). Situations causing an increased leakage from cells or cell death lead to elevated serum LDH levels. The reason for the increase in LDH activity associated with cancer is still unknown.

In the present study we compared LDH with HCG in respect of their clinical usefulness as tumour markers for seminomas. The two markers were analysed with regard to sensitivity and specificity, diagnostic value, response monitoring, follow-up and prognostic value.

Patients and Methods

A total of 105 patients treated for pure seminomatous germ cell tumours (testicular 104, extragonadal 1) between 1980 and 1987 were studied (Table 1); 981 blood samples from various periods of the patients' clinical course were analysed for serum HCG and LDH (per patient: median 7, range 1–44).

Table 1 Details of Patients

	Clinical stage	*No. of patients*	*Mean age ± SD* (years)*
Group 1	I	25	
	IIA-B	5	
	IIC-D	22	38 ± 10
	III	6	
	IV	4	
	Total	62	
Group 2	I	28	41 ± 9
	IIA-B	8	
	IIC-D	22	
	III	9	42 ± 13
	IV	4	
	Total	71	
Group 3	IIB	4	
	IIC-D	24	
	III	10	41 ± 12
	IV	5	
	Total	43	
Group 4	I	9	
	IIA-B	6	
	IIC-D	2	41 ± 10
	III	5	
	Total	22	
Group 5	IIC-D	25	
	IIIB-C	11	40 ± 11
	Total	36	

* SD: Standard deviation

Staging was performed according to the Royal Marsden staging system (Peckham *et al.*, 1979) based on clinical examination, chest X-ray and bipedal lymphography and/or abdominal CT. As a rule, all patients with clinical stage (CS) ≤ IIB received high voltage abdominal radiotherapy as definitive treatment (Fosså *et al.*, 1988). Advanced disease (CS > IIB) was treated by cisplatin-based chemotherapy followed by radiotherapy, surgery and/or additional chemotherapy (Fosså *et al.*, 1987).

According to the period for which serum samples were available, the patients were grouped as follows (Table 1):

Group 1: Patients with pre-orchiectomy samples available.
Group 2: Patients with post-orchiectomy samples available prior to treatment.
Group 3: Patients with advanced seminoma and with samples available before and after chemotherapy.
Group 4: Patients relapsing after initial cytotoxic therapy and samples available at the time of relapse.
Group 5: Patients with CS IIC-IIIC with samples available prior to treatment.

In Groups 1, 2 and 4 the diagnostic value of LDH and HCG was considered. In Group 3 the tumour markers' ability to monitor the response to treatment was examined. The prognostic value of LDH and HCG was investigated in Group 5.

A control group consisted of 22 patients referred to the Norwegian Radium Hospital for testicular lesions other than cancer. All were suspected of having testicular cancer until explorative surgery and biopsy showed a benign histology. The final diagnoses of the 22 patients are given in Table 2.

Table 2 Details of Control Group

Diagnosis	*No of patients*
Haematoma	1
Orchitis/epididymitis	7
Adenomatoid tumour	2
Degenerative changes of tunica vaginalis	8
Hydrocele/spermatocele	2
Necrosis/atrophy	2
Total	22

Biochemical methods

HCG concentrations in serum were determined by a conventional RIA using beta-HCG specific polyclonal antibodies as described elsewhere (Paus *et al.*, 1987, 1988). The cross-reactivity with LH was 0.2%. The reference limit for elevation has been established at 10 u/l. Serum levels of HCG < 200 u/l were considered separately from higher levels.

Serum LDH levels were determined by measuring the decrease in absorption by NADH at 340 nm as pyruvate is reduced to lactate. Assay conditions were optimal as recommended by the Committee on Enzymes (1974). No isoenzyme determinations were undertaken. At our hospital an LDH concentration >450 iu/l is considered elevated.

Statistics

The predictive value, sensitivity and specificity were determined according to Vecchio (1966). The distributions of values were compared with each other by the Wilcoxon test. The chi-squared test evaluated frequency distributions. Relapse-free survival was evaluated by the log rank method (Peto *et al.*, 1977). A *p* value <0.05 was regarded as statistically significant.

Results

Control group

All 22 patients with benign testicular lesions had serum HCG levels below 5 u/l; 6 had LDH levels above the upper limit of the normal range (450 iu/l) but none was above 550 iu/l.

Predictive value, sensitivity and specificity

Of the 981 samples obtained from seminoma patients, 576 were taken from patients with no evidence of disease (NED), 405 were taken when detectable disease was evident (ED = evidence of disease). Of the 576 NED samples, 39 (7%) were elevated for LDH. There was no elevation of HCG (Table 3, Fig. 1). Unexplained false positive LDH values were observed both early and late during the history of the disease. Only 4 of the 39 were substantially increased, using an arbitrary limit of 550 iu/l; 1 of these 4 samples was obtained from a patient who died 2 days later of post-operative complications, 1 was re-evaluated in a new blood sample and then found to be within the normal range. No reasonable explanation was found for the 2 remaining elevated LDH values in patients with NED.

The values for specificity and sensitivity and the predictive values for a positive test for both markers are shown in Table 4.

Table 3(A) Serum LDH and HCG in Patients Without Evidence of Disease

LDH (iu/l)	*HCG (u/l)* *< 10*
	< 10
< 450	537
450–< 550	35
≥ 550	4
Total	576*

* No HCG levels ≥ 10 u/l were found.

Table 3(B) Serum LDH and HCG in Patients with Evidence of Disease

	HCG (u/l)			
LDH (iu/l)	*< 10*	*10–< 200*	*≥ 200*	*Total*
< 450	181	26	9	216
450–< 550	35	6	4	45
≥ 550	60	68	16	144
Total	276	100	29	405

Group 1. Pre-orchiectomy samples

Seven of 25 patients with CS1 (28%) had elevated serum LDH before orchiectomy and 3 of them had serum levels above 550 iu/l (Fig. 1A). Ten CSI patients (40%) had HCG levels above normal (Fig. 1B). In 56% of the patients either LDH or HCG or both tumour markers were elevated pre-operatively.

Of 23 patients with advanced disease, 16 were HCG-positive pre-operatively (70%); 1 patient had an LDH value between 450 and 550 iu/l and 17 were significantly elevated using 550 iu/l as a limit. In advanced seminomas the frequency of at least one marker being elevated increased from 70 to 78% when using both the HCG and LDH assay.

Patients with advanced seminoma had significantly higher pre-orchiectomy values of serum

Table 4 Specificity, Sensitivity and Predictive Value of Elevated LDH and HCG in Seminoma

	HCG *(%)*	*LDH* *(%)*
Specificity	100	93.2
Sensitivity	31.9	46.7
Predictive value*	100	82.9

* Of positive tests.

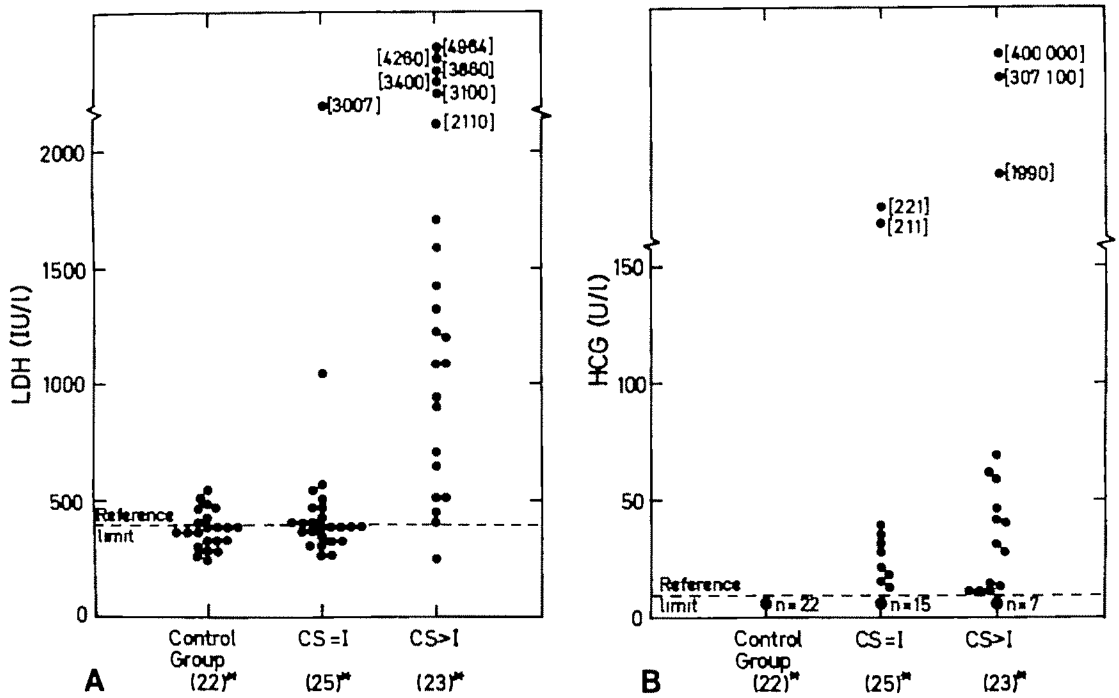

Fig. 1 Pre-orchiectomy serum LDH (A) and HCG (B) in patients with seminoma and in patients with benign testicular lesions (control group). ( )* Number of patients within a group

LDH and HCG compared with patients with CSI ($P<0.001$ for both markers). No statistical difference was found between the control group and CSI seminoma patients with regard to the degree of LDH elevation.

Group 2. Post-orchiectomy samples

None of the 28 orchiectomised seminoma patients with CSI had elevated serum LDH or HCG. After orchiectomy, 35 of 43 patients (82%) with advanced seminoma had LDH values >450 iu/l. Only 17 of these 43 patients (40%) had increased serum HCG (Table 5). Serum HCG levels ≥200 u/l were most often found in patients with very advanced disease (Stage IIC: 1, Stage IIIC: 2, Stage IV: 2).

Group 3. Monitoring during chemotherapy

Cisplatin-based combination chemotherapy was given to 43 patients as induction treatment; as a rule, this was followed by radiotherapy, surgery and/or additional cytotoxic treatment in some cases (Fosså *et al.*, 1987); 35 patients received 4 cycles, 5 received 3 cycles and 3 patients had only 1 cycle. The extent of disease was assessed (by clinical, radiological and/or surgical means) before starting treatment and 3 to 4 weeks after chemotherapy, together with analysis of serum LDH and HCG.

Complete remission was noted in 37 patients after chemotherapy; 7 of these (19%) were initially LDH-negative and remained so. In 23 of the remaining 30 patients (77%) the elevated pretreatment LDH decreased to the normal range during chemotherapy, but 7 LDH values remained above normal at the end of chemotherapy. The serum levels in 4 of these patients became normal during subsequent radiotherapy; 2 have remained elevated throughout tumour-free follow-up. No follow-up information is available in the seventh patient, who died tumour-free after the first chemotherapy cycle due to toxicity. The LDH levels in 6 patients were normal in spite of clinical/radiological signs of tumour persistent after chemotherapy.

Table 5 Serum LDH and Serum HCG in 43 Orchiectomised Patients with Advanced Seminoma before Further Treatment

	HCG (u/l)			
LDH (u/l)	*<10*	*10–<200*	*≥200*	*Total*
<450	7	1	0	8
450–<550	3	0	0	3
≥550	16	11	5	32
Total	26	12	5	43

Of the 37 patients with a complete response (CR), 16 (43%) had elevated HCG levels before treatment. All CR patients had normal HCG levels after a maximum of 2 cycles and at the end of their chemotherapy (Fig. 2); 4 of the 6 patients with evidence of residual tumour had elevated HCG after initial chemotherapy; 2 patients were subsequently rendered tumour-free by additional treatment, as confirmed by normalisation of HCG. The 2 other patients developed resistant disease (with a further increase in HCG).

Falsely elevated LDH levels were thus found in 7 of 37 tumour-free patients (19%) but no raised HCG levels were observed in patients with NED; 6 patients with evidence of tumour after chemotherapy had normal LDH; 4 of them had elevated HCG but HCG was normal in the remaining 2.

Group 4. Relapsing patients

Twenty patients relapsed 25 times, *i.e.* 3 patients relapsed twice and 1 had 3 recurrences. In 23 of the 25 relapses both LDH and HCG were assessed at the time when recurrence of disease was diagnosed (Table 6).

Increased LDH activity in serum accompanied 16 incidences of relapse (64%), 13 of which were elevated above 550 iu/l; 11 cases of relapse were associated with an elevated serum HCG (48%). The proportion of marker-positive recurrences increased from 39 to 70% when LDH was measured in addition to HCG.

Table 6 Serum LDH and HCG in Seminoma Patients at Time of Diagnosis of Recurrence after Previous Cytotoxic Treatment

	HCG (u/l)			
LDH (iu/l)	*< 10*	*10–< 200*	*> 200*	*Total*
< 450	5	1	1	7
450–< 550	3	0	0	3
≥ 550	4	8	1	13
Total	12	9	2	23

Group 5. Prognostic significance

There was no significant difference in recurrence-free survival when comparing 19 initially HCG-negative patients with 17 patients who had elevated (≥ 10 u/l) pre-treatment HCG levels (P: 0.17) (Fig. 3A). Using 40 u/l as a borderline, there was a trend towards higher significance (P: 0.10). The recurrence-free survival in patients with HCG-producing seminoma tended to be worse than in HCG-negative patients; 2 of the 5 patients with initial serum HCG ≥ 200 u/l died from their disease.

In the same 36 patients, relapses occurred in 2 of 5 initially LDH-negative patients following cytotoxic chemotherapy. Two of 31 LDH-positive

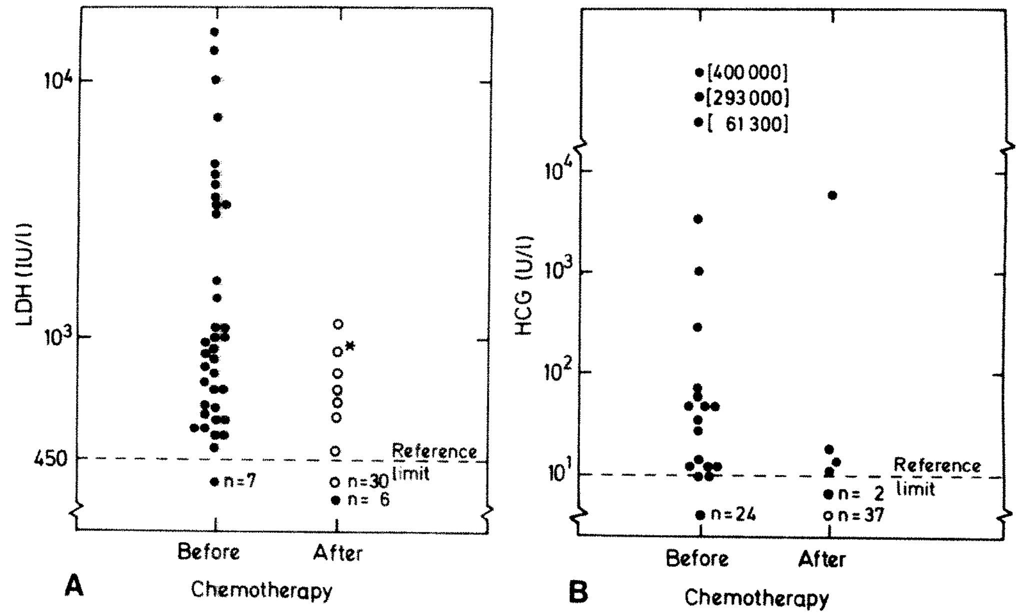

Fig. 2 Serum LDH (A) and HCG (B) before and after cisplatin-based chemotherapy in patients with advanced seminoma. ● Patients with evidence of disease. ○ Patients without evidence of disease. * Patient dead of treatment-related toxicity, tumour-free at autopsy.

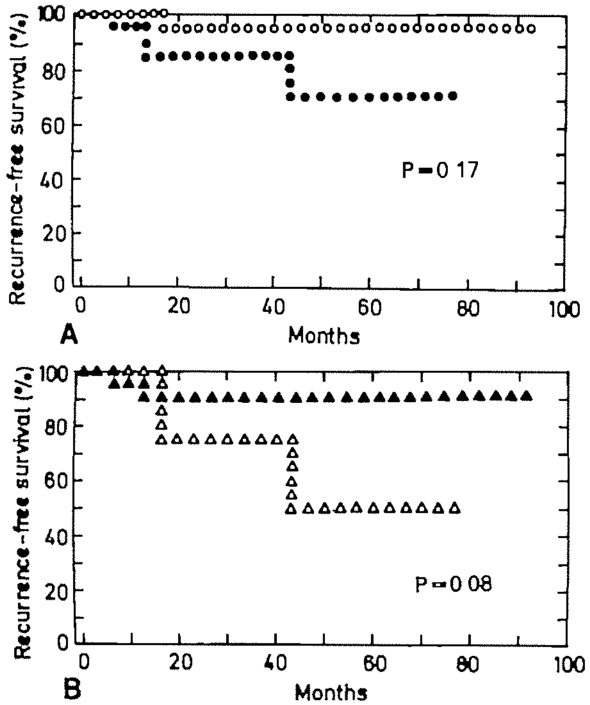

Fig. 3 (A) Recurrence-free survival in 36 seminoma patients with stage IIC-IIIC ○ Pre-treatment HCG < 10 u/l (17 patients); ● Pre-treatment HCG > 10 u/l (19 patients) (B) Recurrence-free survival in 36 seminoma patients with stage IIC-IIIC △ Pre-treatment LDH ≤ 450 iu/l (5 patients), ▲ Pre-treatment LDH > 450 iu/l (31 patients)

patients developed recurrences. There was a trend towards a poorer prognosis for LDH-negative patients, although the difference did not reach statistical significance (P: 0.08) (Fig. 3B).

Discussion

Sensitivity and specificity

Both serum LDH and HCG are useful in predicting the presence of active disease in patients with a history of pure seminoma. LDH has, however, a lower specificity than HCG. By definition, 2.5% of LDH and HCG samples taken from disease-free patients must be expected to be above the upper limit of the normal range. However, falsely elevated levels were found only for LDH (7%) but not for HCG. Our study shows that moderately elevated serum LDH levels do not necessarily indicate tumour activity in seminoma patients. This is in agreement with the findings of Taylor *et al.* (1986), who reported that 25% of 92 patients presented with falsely elevated LDH activity during early follow-up.

Diagnosis

This study indicates that slightly elevated serum LDH (< 550 iu/l) cannot discriminate patients with seminoma CSI from patients with benign testicular lesions who are suspected of having testicular cancer. Von Eyben *et al.* (1983) (in 5 of 11 patients) and Zontag (1964) (in 5 of 5 patients) reported LDH-1 to be the most frequently elevated isoenzyme in seminomas. LDH-1 is normally absent in testicular tissue (Goldberg, 1977). In the diagnostic situation, therefore, the determination of LDH isoenzymes may be more useful than the analysis of total LDH activity. On the other hand, a substantial pre-orchiectomy elevation of LDH in a patient with a testicular lesion strongly indicates advanced testicular seminoma (von Eyben *et al.*, 1983; Lange and Winfield, 1987). Any serum HCG elevation in patients with testicular lesions should be considered decisive for the diagnosis of testicular cancer. The distinction between seminoma and non-seminoma can, of course, only be made on a histological basis.

Treatment monitoring and follow-up

In most patients with advanced seminoma, both LDH and HCG accurately reflect the response to treatment. Taylor *et al.* (1986) found that serum LDH precisely monitored the response to chemotherapy in all of 10 patients with advanced seminoma. There are, however, exceptions to this general rule. In our Group 3, 6 patients with known residual tumours had normal LDH levels at the end of chemotherapy in spite of raised pre-treatment LDH and falsely elevated LDH levels found in 7 patients. LDH values are therefore not reliable in monitoring response to treatment and must be interpreted with caution. On the other hand, any HCG elevation or increase during or after chemotherapy indicates disease activity.

This series shows the usefulness of both LDH and HCG as tumour markers during post-treatment follow-up, especially if both markers are combined; 70% of patients who relapsed presented with elevated LDH, HCG or both.

Prognostic value

The prognostic significance of HCG in seminoma has been the subject of much debate (Javadpour *et al.*, 1978; Mauch *et al.*, 1979; Lange *et al.*, 1980; Mostofi, 1980; Morgan *et al.*, 1982; Swartz *et al.*, 1984; Butcher *et al.*, 1985; Ford *et al.*, 1985; Mirimanoff *et al.*, 1985). Some oncologists have argued that HCG elevation probably reflects a more dedifferentiated state of the tumour and may therefore predict a poor prognosis. Morgan *et al.* (1982) found elevated serum levels of HCG to relate to a poor prognosis. Immunohistochemically detectable beta-HCG containing cells, the presence of syncytiotrophoblastic cells (Mostofi, 1980) and the occurrence of gynaecomastia (van der Werf-Messing, 1971) have been shown to worsen the prognosis in seminoma patients. Such prognostic studies are not always carried out in patients with similar stage and treatment and such heterogeneity may explain the prognostic differences. Nevertheless, the present series of comparable patients also shows a trend towards poor prognosis in comparable patients with HCG-positive advanced seminoma. The few patients with initial serum HCG ≥ 200 u/l seem to have a particularly poor prognosis.

LDH elevation has been reported to be a sign of poor prognosis in advanced non-seminomatous testicular cancer (Lippert and Javadpour, 1981; Bosl *et al.*, 1983) and in a limited series of patients with metastatic pure seminoma (von Eyben *et al.*, 1983). Contrary to what was expected from these reports, we could not confirm the dismal effect of pre-treatment LDH elevation in 36 seminoma patients with IIC-IIIC disease.

Serum LDH does not fulfil several requirements for an ideal tumour marker for seminomatous germ cell tumours. Its relatively high sensitivity of positive values must be balanced against the < 100% specificity. These limitations are of particular clinical significance at the time of diagnosis of early seminoma and when monitoring chemotherapy of advanced seminoma. LDH seems to have some clinical usefulness in detecting relapses during follow-up.

The use of serum HCG as a tumour marker is limited by low sensitivity of a positive value. Serum HCG determinations are of diagnostic significance in 50% of all seminoma patients before orchiectomy and it reliably monitors the response to treatment. HCG elevation during follow-up is highly suggestive of relapse. The need remains to find more specific and more sensitive tumour markers to improve the clinical management of seminoma patients.

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Prospective Study of Routine Scrotal Ultrasonography in Urological Practice

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Summary—The value of routine scrotal ultrasonography has been evaluated in a prospective study of 109 men with scrotal symptoms or signs. Ultrasonography had a sensitivity of 100% and specificity of 99% for testicular tumour. Clinically useful information was provided in 53% of patients and 8% might have avoided surgery if the ultrasound report had been heeded. Ultrasonography did not provide any additional information in patients with scrotal pain and an entirely normal scrotum clinically, and in those with epididymal cysts in whom the testis was palpably normal. If these 2 groups had been excluded from routine scrotal ultrasonography there would have been a 25% reduction in the number of examinations without any reduction in diagnostic yield.

Since the first description of scrotal ultrasonography (Miskin and Bain, 1974) there have been numerous reports on the ultrasonographic appearances of a variety of scrotal pathologies. Fowler *et al.* (1987) suggested that ultrasonography should be performed on all patients with scrotal symptoms or signs. Routine scrotal ultrasonography places a significant burden on radiology services and the purpose of this prospective study was to determine whether it could be limited to certain groups of patients without any reduction in diagnostic yield.

Patients and Methods

During a 14-month period 109 men underwent scrotal ultrasonography; their median age was 32 years (range 16–80); 84 were seen as out-patients and 25 as emergencies; 57 presented with an increase in scrotal size as their primary symptom, 47 with scrotal pain and 5 had suffered scrotal trauma. The final diagnosis (Table 1) was based on operative findings in 36 men and by at least 12 months' follow-up in the remainder.

The scrotal contents were examined using a curved linear array 5 MHz transducer. Longitudinal, transverse and oblique scans were obtained with an acoustic coupling gel placed on the anterior scrotum. Scrotal ultrasonography had only recently been introduced into this department and it was decided therefore that clinical decisions would be based upon the results of physical examination, although as the study progressed the results of

Table 1 Summary of Final Diagnoses

	Primary symptom		
Final diagnosis (n=109)	*Increase in scrotal size (n=57)*	*Scrotal pain (n=47)*	*Scrotal trauma (n=5)*
Epididymal cyst	20	6	0
Hydrocele	17	0	1
Normal scrotum	10	19	2
Testicular tumour	6	0	0
Sperm granuloma	1	1	0
Testicular cyst	1	0	0
Inguino-scrotal hernia	1	0	0
Epididymitis	0	9	0
Epididymo-orchitis	1	4	0
Varicocele	0	4	0
Necrotic testis	0	2	0
Epididymal abscess	0	1	0
Granulomatous orchitis	0	1	0
Shattered testis	0	0	2

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scrotal ultrasonography were increasingly taken into consideration. As the ultrasound features of torsion may be indistinguishable from those of inflammation (Bird *et al.*, 1983), patients with acute scrotal pain only had an ultrasound examination once the decision to operate or not had been made. If it was decided to operate, ultrasonography was performed providing it did not delay surgery.

Results

Patients presenting with increase in scrotal size (n=57)

Ultrasonography was requested in these patients in order to determine:

1. Whether or not a scrotal mass was a testicular tumour (n=23).
2. If a cystic swelling was caused by an epididymal cyst or a hydrocele (n=17).
3. Whether there was a testicular tumour underlying a hydrocele (n=12).
4. If a scrotum which felt normal clinically appeared normal ultrasonographically (n=5).

In the first group of patients, ultrasonography correctly diagnosed 6 testicular tumours (4 seminomas, 2 teratomas), 8 epididymal cysts, 5 normal testes, 1 sperm granuloma, 1 testicular cyst and 1 hydrocele. There was 1 false positive for tumour in a young man with an inguino-scrotal hernia in whom the testis was surrounded by omentum and therefore appeared abnormal on ultrasound. Ultrasonography correctly differentiated epididymal cyst from hydrocele in all of the patients in group 2. There were 11 normal testes and 1 infected hydrocele correctly identified by ultrasound in group 3, and 5 testes in group 4 which appeared normal on ultrasound remained normal 1 year later.

It was felt that ultrasonography had provided useful information in 35 (67%) of the 57 patients in this group; 6 men might have avoided operation if the ultrasound report had been heeded.

Patients presenting with scrotal pain (n=47)

Twenty men were admitted as emergencies and 27 were seen as out-patients. Ultrasonography did not provide any additional information in 17 patients who had an entirely normal scrotum on clinical examination; 30 patients had an enlarged and/or tender scrotum and ultrasonography provided additional or useful information in 18 (Table 2). Three men might not have been operated on if the ultrasound report had been observed.

Patients presenting with scrotal trauma (n=5)

Ultrasonography provided valuable information in all of these patients, correctly identifying 2 shattered testes, 2 normal testes and one reactive hydrocele.

In summary, ultrasonography had a sensitivity of 100% and specificity of 99% for testicular tumour. The overall diagnostic accuracy was 95%. Clinically useful information was provided in 58 patients (53%) and 9 (8%) might not have been operated on had the ultrasound report been observed.

Discussion

Specific indications for scrotal ultrasonography include cryptorchidism (Hederstrom *et al.*, 1985), gynaecomastia (Hendry *et al.*, 1984), occult metastatic carcinoma (Kirschling *et al.*, 1983), follow-up of the remaining testis after orchiectomy for tumour (Scott *et al.*, 1986), infertility (McClure and Hricak, 1986) and testicular screening in patients with leukaemia (Bland *et al.*, 1986) or neuroblastoma (Casola *et al.*, 1984). The purpose of this study, however, was to evaluate the role of scrotal ultrasonography in routine urological practice. The operation rate, final diagnoses and incidence of testicular tumour were remarkably similar to those of other studies (Valvo *et al.*, 1983; Desai *et al.*, 1985; Rifkin *et al.*, 1985), suggesting that our patients were representative of those generally seen in urology departments.

Although some men with scrotal pain had an enlarged scrotum and vice versa, the classification of patients according to their primary presenting symptom allowed a rational assessment of the indications for and results of ultrasonography. The final diagnosis in a proportion of those patients who were not operated on must remain speculative, but

Table 2 Comparison of Clinical and Ultrasonographic Diagnoses in 18 Men with Scrotal Pain in whom Ultrasonography Provided Useful Information

Putative clinical diagnosis	*No of patients*	*Ultrasound diagnosis*	*No. of patients*
Epididymitis	12	Epididymitis	4
		Normal	4
		*Small epididymal cyst	2
		Sperm granuloma	1
		Varicocele	1
Epididymo-orchitis	4	Normal	2
		Necrotic testis	1
		*Granulomatous orchitis	1
Varicocele	1	Varicocele	1

* See text.

the fact that they were followed up for at least 1 year makes it unlikely that any serious pathology was missed. Since scrotal ultrasonography had only recently been introduced into this department it was decided that patient management would be based upon the findings on physical examination. This allowed an estimate of the number of cases in which the ultrasound findings would have contributed to or altered the clinical assessment. However, it quickly became apparent that scrotal ultrasonography was very accurate and its findings were therefore increasingly taken into account.

Our findings confirm that scrotal ultrasonography is very sensitive for testicular tumour. We had only 1 false positive for tumour even though the ultrasound appearances of orchitis, torsion and infarction may be indistinguishable from those of malignancy (Carroll and Gross, 1983; Hricak and Filly, 1983). It is important to note in this context that epididymal enlargement cannot be used as a criterion to differentiate malignant from benign disease (Worthy *et al.*, 1986) and that epididymal cysts can compress the testis and produce ultrasonographic appearances suggestive of malignancy (Rifkin and Brownstein, 1983). Hydroceles, which are present in 3% of patients with testicular tumours (Nilsson *et al.*, 1980), preclude adequate examination of the scrotum and all of these patients should therefore have ultrasonography. We found that ultrasonography could reliably distinguish hydrocele from epididymal cyst. This information is of clinical value since it has been reported that hydroceles respond more frequently than epididymal cysts to injection sclerotherapy (Michell *et al.*, 1985). We do not think there is a specific indication for scrotal ultrasonography in men with epididymal cysts or spermatoceles and an easily palpable normal testis; 5 patients whose presenting symptom was an increase in scrotal size appeared clinically to have a normal sized testis. Scrotal ultrasonography not only reassured these patients but also excluded the presence of a testicular tumour in a previously atrophic testis which had enlarged to a "normal" size.

The overall diagnostic accuracy of ultrasonography was 95%. This figure is similar to that of other studies, but it should be remembered that because the ultrasound features of torsion may be indistinguishable from those of inflammation (Bird *et al.*, 1983) we have not routinely scanned patients with acute scrotal pain. Ultrasonography did not provide additional information in those men with pain and a clinically normal scrotum and we feel that these patients do not routinely require ultrasonography. It should be noted that we included in the abnormal group those men whose only abnormality on examination was tenderness. This is important because tenderness precludes an adequate examination and is thus an indication for ultrasonography. Although 10% of patients with tumours present acutely with pain (Martin and Carte, 1987), the scrotum is always abnormal clinically. We have been unable to find a report of a patient with a testicular tumour presenting with pain and an entirely normal scrotum on clinical examination.

Ultrasonography provided additional information in 64% of patients with pain and an abnormal scrotum (Table 2). Although ultrasonography was unable to make a specific diagnosis in some of these patients, it did alter or expedite their management. This is illustrated by the patient with granulomatous orchitis who presented acutely with scrotal pain. At follow-up 2 weeks later, physical examination revealed generalised testicular tenderness, ultrasonography showed a "diffusely abnormal echo pattern, although likely to be due to orchitis tumour cannot be excluded". As a result of this ultrasound report the scrotum was explored and an orchiectomy performed. Histology showed granulomatous orchitis. Thus although ultrasonography did not make the specific diagnosis of granulomatous orchitis (Scott and Bayliss, 1985), it undoubtedly hastened this man's treatment. Two patients who presented with scrotal pain were shown by ultrasonography to have small cysts in the epididymal head. Epididymal cysts are painless and were not therefore the cause of their pain, which settled with conservative treatment. The value of ultrasonography in these cases was that it revealed the cause of the palpable clinical abnormality and saved these patients from further investigation and possible operation.

Ultrasonography is helpful in the management of the injured scrotum (Anderson *et al.*, 1983) and it correctly diagnosed 2 ruptured testes and 1 traumatic hydrocele in our patients. It is not possible, using ultrasound, to differentiate haematocele from exudative hydrocele (Schaffer, 1985) and any fluid collection that entirely encircles the testis should therefore be explored and drained.

In conclusion, this study confirmed the high diagnostic accuracy of scrotal ultrasound for diagnoses other than testicular torsion. It did not provide additional information in men with epididymal cysts and a palpably normal testis or in men with pain and an entirely normal scrotum. If these patients had been excluded from routine ultrasonography, the number of examinations would have been reduced by 25% without any reduction in diagnostic yield. For this policy to be safely introduced into urological practice patients must be examined by an experienced clinician, and those with scrotal masses other than obvious epididymal cysts should have an ultrasound examination.

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Gynaecomastia and Occult Leydig Cell Tumour of the Testis

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Summary—Two patients with Leydig cell tumours of the testis are described. Both presented with gynaecomastia, but on initial examination had apparently normal testes. The causative tumour did not become obvious for some months, despite being carefully sought. Review of the literature suggests that gynaecomastia preceding a readily palpable tumour is a recognised problem.

The detection and management of Leydig cell tumours of the testis are discussed.

Testicular tumours are rare in the general population, occurring at a rate of about 2/100,000 *per annum*. Because of their peak incidence in the third decade of life, however, they present more commonly in military personnel. Leydig cell tumours of the testis are even rarer and account for only 2% of all testicular tumours. These tumours are of interest because of their potentially feminising effect on adult males.

In a United States Armed Forces review of testicular tumours, 10% presented with gynaecomastia (Dixon and Moore, 1952), whilst in a more recent British army review 5% presented with gynaecomastia (Stephen, 1958).

Although few soldiers presenting with gynaecomastia have testicular tumours, this report describes 2 soldiers presenting with gynaecomastia who later proved to have Leydig cell tumours of the testis.

Case Reports

Case 1. APP. H. This 18-year-old recruit was referred for investigation of exercise-induced asthma. He also complained of bilateral gynaecomastia but no testicular abnormality was discovered. Oestrogen estimations at this time were normal. At his next review 2 months later, a firm swelling was found in the upper pole of the left testis. He was referred to the surgeons and the left testis was explored via the groin, occluding the cord prior to mobilisation. A firm 1-cm tumour was found in the upper pole of the testis. The testis and cord were excised and sent for histological examination. The testis was reported to contain a well circumscribed Leydig cell tumour, with no invasion locally or spread to the cord. Since there was no evidence of other metastasis, no further treatment apart from regular follow-up was deemed necessary.

The gynaecomastia disappeared spontaneously over the following 3 months. The patient remains well 4 years after initial presentation and has been fitted with a prosthetic testis.

Case 2. SGT E. This 35-year-old man presented to his Regimental Medical Officer with unilateral painful gynaecomastia on a number of occasions over 6 months, on the last of which he was noted to have a rather firm left testis. The testis had previously been described as normal. In addition to a tender, prominent breast disc on the left, he was found to have a rather firm left testis with a hard, nodular epidydimis. The latter could have been consistent with epidydimitis. Since the gynaecomastia was quite uncomfortable, he was taken to theatre with a view to excising the breast disc and exploring the testis.

The testis was explored through the groin and again looked normal apart from a nodular epidydimis, although it felt rather tense. It was sagittally sectioned with the cord occluded, and a 1-cm yellowish nodule was found within its substance. The testis and cord were excised and sent for histological examination, as was the breast disc. In this case the tumour had a solid tubular arrangement consistent with Sertoli cell tumour; however, a final diagnosis of Leydig cell tumour was made because it had microvacuolisation of the cytoplasm and

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a few Reinke crystals, said to be pathognomic of Leydig cell tumour.

Since there was no evidence of local or distant spread, no further treatment apart from regular follow-up was deemed necessary.

The patient remains well 4 years after presentation.

Discussion

The Leydig or interstitial cells of the testis are responsible for producing testosterone, but also produce oestrogen and its derivatives. The benign tumour usually consists of uniform cells with a round or oval nucleus and abundant eosinophilic cytoplasm. The feminisation with which these tumours present may be due directly to oestrogen production or indirectly to breakdown of excess androgen produced by the tumour cells. The latter was, presumably, the cause of gynaecomastia in Case 1.

It must be stressed that Leydig cell tumours of the testis are extremely rare, accounting for 2% of testicular tumours. Unlike the majority of testicular tumours, they have occurred in patients aged between 2 and 90 years (mean 60) (Mahon *et al.*, 1973). In the pre-pubertal group they may present with precocious puberty, macrogenitosomia and hirsutism. Gynaecomastia may also be present but is often masked by the virilising features. In adults, 90% of these tumours are benign and 20% of patients present with gynaecomastia (Gabrilove *et al.*, 1975). Although cellular anaplasia, increased mitoses and vascular invasion are suspicious features, metastasis is the only certain criterion of a malignant Leydig cell tumour. Metastasis should be suspected if there is a persistent elevation of oestrogens following orchiectomy. Gynaecomastia may persist or reappear (Siegel and Thomas, 1984) or indeed appear for the first time (Gabrilove *et al.*, 1975; Davis *et al.*, 1981) when metastasis occurs.

Patients presenting with gynaecomastia must have their testes carefully examined. If there is an obvious testicular swelling this should be explored via a groin incision. Should the testes feel normal, ultrasound examination has been advocated (Emory *et al.*, 1984; Hendry *et al.*, 1984). Three cases were described where an otherwise impalpable tumour was detected with ultrasound. Siegel and Thomas (1984) reported a young man being investigated for gynaecomastia where both ultrasound and needle biopsy failed to detect a Leydig cell tumour which became clinically apparent some months later.

Thus, although ultrasound examination of the testis may be helpful, any suspect testis should be explored, blood having been taken for tumour marker estimation. The patient should be warned that he might require orchiectomy.

At operation, even if the testis appears superficially normal, it may be sectioned sagittally on the anterior border opposite the entrance of its blood supply without permanently damaging the testis, should it prove to be normal. This may be the only reliable method of detecting these tumours in their early stage.

Management of the patient following orchiectomy poses problems for which little advice is available because of the rarity of Leydig cell tumours. The only definite criterion for malignancy is metastasis, and this may be delayed for as many as 9 years (Silverberg *et al.*, 1963).

Metastasis generally presents with endocrine manifestations (Lockhart *et al.*, 1976). Once metastasis occurs, its control by radiotherapy and chemotherapy is disappointing (Shapiro *et al.*, 1984). Parker (1958) reported successful resection of pulmonary metastases in 2 cases. In only one-third of cases does gynaecomastia resolve spontaneously, despite apparent cure (Gabrilove *et al.*, 1975).

In conclusion, the 2 cases presented and a review of the literature suggest that gynaecomastia may precede detection of the causative testicular tumour by many months. Ultrasound examination, although useful for detecting a small tumour, is not infallible.

Careful follow-up of males presenting with gynaecomastia for up to a year is recommended.

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Azoospermic Infertile Men

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Summary—Of 1518 consecutive cases of men referred with infertility, 369 (24%) had complete absence of spermatozoa from their semen (azoospermia). This is a high incidence compared with the rates of 4 to 14% reported in other studies. Primary testicular failure, ductal obstruction, endocrine abnormalities, cryptorchidism and infection were common findings in these men; 247 (67%) gave a history of sexually transmitted infection. The duration of involuntary infertility on presentation ranged from 1 to 16 years. Very few couples accepted artificial insemination with donor semen (AID) as a method of achieving pregnancy and none would consider adoption.

Azoospermia has a grave prognostic significance in the evaluation of male fertility. In the indigenous Zimbabwean male it is considered an emotionally devastating condition which is difficult to accept since women are traditionally always blamed for infertility.

Men only agree to investigation and treatment as a last resort. Also, society stigmatises and exerts considerable pressure on couples who remain childless. This presents a serious psychological burden which can lead to family break-up.

While the investigation of azoospermic patients aims at establishing the aetiology of the abnormality, in many instances the available treatment is ineffective and the prognosis remains poor. Where attempts to correct the condition are not successful, it is important to discuss the prognosis and offer alternative methods of management such as AID or adoption.

In a study of 285 male partners of consecutive couples reporting for infertility in Scotland, Hunter *et al.* (1974) reported a 7% incidence of azoospermia. None of the patients in their study had chromosomal disorders, while FSH levels showed a bimodal distribution. In another study of 740 infertile men, Jequier and Holmes (1984) found 13.6% to have obstructive azoospermia associated with chronic respiratory disease. David *et al.* (1973) reported a much lower prevalence of azoospermic infertile cases (7.4% of 3119 couples).

In Nigeria, Awojobi *et al.* (1983) found 60 of 610 infertile men (12%) to be azoospermic, while in the United States Toth *et al.* (1984) found only 4% to be azoospermic in a study of 1350 infertile couples.

The present study sought to define the characteristic features associated with azoospermia in men presenting with infertility in Zimbabwe.

Patients and Methods

Male partners of 1518 couples presenting for investigation of fertility were referred to an Andrology Clinic for further study after deficiencies in semen were found; 80 male partners of pregnant women served as controls. All of the referred men completed a questionnaire on age, marital status, duration of infertility, occupation, medical and sexual history. The men were instructed to collect masturbation semen specimens into clean, wide-mouthed containers. The semen was analysed for sperm density, motility, pH, morphology, viscosity and appearance using WHO (1980) recommended procedures. Bacterial cultures were performed on semen aerobically on MacConkey agar and anaerobically in chocolate culture medium.

Blood samples were collected by venepuncture, after a period of rest, and analysed for luteinising hormone (LH), follicle stimulating hormone (FSH), prolactin and testosterone, using clinical assays

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kits. A clinical examination was carried out to exclude gross physical problems and the Prader orchidometer was used to determine testicular size. Testicular biopsies were performed in azoospermic patients with normal FSH using techniques described by Girgis and Hafez (1977). Testicular exploration, including vasography, was performed in patients with testicular size $< 10\ \text{cm}^3$. Twelve patients were investigated for the presence of Barr bodies as well as a full chromosome investigation based on metaphase spread from cultured peripheral blood lymphocytes using the Difco laboratories kit method (Michigan, USA). The significance of differences in values compared between groups was assessed using the *t* test where appropriate and approximate confidence intervals.

Results

Of the 1518 men investigated, 369 (24%) had azoospermia following a minimum of 3 semen analyses at 2-weekly intervals. This incidence was compared with those reported in the literature (Table 1). The men were studied in terms of general features, testicular pathology, endocrine profile, cryptorchidism, varicococele and other conditions.

General features

The mean age of patients presenting with azoospermia was 33.6 ± 6.8 years (mean ± SD) and the mean age for the controls was 31.5 ± 7.0 years (mean ± SD). It was of note that professional drivers constituted the largest single occupational group (n = 36: 10%) amongst the azoospermic men. They were followed by machine operators (n = 14: 4%) and welders (n = 6: 2%). Five patients reported working with various chemical agents. The majority of couples had been childless for 7 or more years and the period of infertility before reporting to the clinic ranged from 1 to 16 years (Table 2).

Table 1 Incidence of Azoospermia

Reference	*Total consecutive cases*	*No. of azoospermic cases*	%
David *et al.* (1973)	3119	230	7.4
Matthews *et al.* (1981)	379	43	11.35
Ojo (1968)	85	90	10.6
Toth *et al.* (1984)	1350	54	4.0
Lipshultz (1980)	200	8	4.0
Chukudebelu (1978)	350	31	8.9
Hunter *et al.* (1974)	285	20	7.0
Awojobi *et al.* (1983)	610	60	12.0
Present study	1518	369	24.3

Table 2 Duration of Infertility at Referral

Years of infertility	*No. of men*	%
1–2	3	1.0
3–4	52	14.0
5–6	64	17.0
7–8	136	37.0
9–10	63	17.0
11–12	42	11.0
13 or more	9	2.0
Total	369	100

Of the men investigated, 67% gave a history of past urogenital infection (including urethral discharge) and 57.6% had had schistosomiasis; 46% admitted to having had syphilis and 16% had a history of orchitis (Table 3).

Staphylococcus aureus was the most common bacterial isolate (28%); 9 patients (2.5%) had *Neisseria gonorrhoea* and *Streptococcus* was cultured from the masturbation samples in 18%.

The mean semen volume in the patients was 1.6 ± 1.2 ml (mean ± SD) and in the controls was 1.8 ± 1.5 ml (mean ± SD). The semen pH of 7.5 to 8.0 in patients and 7.6 to 7.9 in controls showed no significant difference.

Testicular pathology and obstructive azoospermia

Primary testicular pathology and obstruction were detected in 310 azoospermic patients (84%). Obstructive azoospermia was present in 43% and azoospermia secondary to impaired spermatogenesis in 41%. The frequency of testicular dysfunction is shown in Table 4.

Reduced testicular volumes ranging from 1 to $10\ \text{cm}^3$ (5.3 ± 3.3, mean ± SD) were present in 87 men (24%). Mean testicular volumes in the fertile men were $17.0 \pm 4.57\ \text{cm}^3$ (mean ± SD); there were

Table 3 History of Single or Multiple Medical Problems

Disease	*No. of patients*	%	*Percentage with obstructive azoospermia*	*Percentage with testicular failure*
Post-pubertal mumps	26	7.28	41.0	57.0
Orchitis	61	16.42	63	30.2
Bilharzia	213	57.66	35.7	26.5
Tuberculosis	7	2.0	55.0	20.0
Gonorrhoea	248	67.29	69.0	43.0
Syphilis	171	46.41	39.1	51.0
Chanchroid	33	8.85	25.0	49.0
Genital injury	1	0.3	—	—
Filaria	0	0.0	—	—

Table 4 Testicular and Post-testicular Pathology Findings in the Azoospermic Men

Pathology	*No of cases*	*% of total*
Reduced testicular volume (range 1–10 cm^3)	87	24.0
Post-testicular ductal obstruction	159	43.0
Germ cell aplasia	33	9.0
Tubular hyalinisation	14	3.8
Sertoli cell only	8	2.2
Thickened basement membrane	6	1.6
Orchitis	3	0.8
Total	310	84

no volumes in the 1 to 10 cm^3 range. Post-inflammatory epididymo-vasal obstruction was present in 159 patients (43%). Germ cell aplasia in testicular biopsies was found in 33 cases (9%).

The other abnormalities were Sertoli cell only, hyalinisation of tubules, maturation arrest, thickened basement membrane, orchitis and fibrotic testes. The incidence of obstructive azoospermia and testicular failure was compared with that reported by others (Table 5).

Endocrine profile

Elevated FSH levels of 46.0 ± 2.34 mIU/ml (mean ± SEM) were found in 144 azoospermic patients (39%) and 10.6% had decreased serum FSH levels of 3.2 ± 0.45 mIU/ml (mean ± SEM) (normal range 5–20 mIU/ml). FSH was elevated in the majority of men with a mean testicular volume less than 10.0 cm^3 and those with testicular maldescent, whereas levels in the controls were significantly lower ($P < 0.001$). The 95% confidence intervals of FSH concentration at mean testicular volumes between 1 and 10 cm^3 were 10.75 to 13.65.

While 206 patients (55.8%) had a raised LH concentration of 43.9 ± 4.87 mIU/ml (mean ± SEM), 10.6% had a low concentration of 3.4 ± 2.8 mIU/ml (mean ± SEM) (laboratory normal range 5–20 mIU/ml). The raised LH also showed a significant difference ($P < 0.001$) from levels in the control men.

While 20.5% of patients had high testosterone levels of 13.8 ± ng/ml, another 20% had a very low serum testosterone concentration of 1.6 ± ng/ml ± 0.15 (mean ± SEM) (normal range 3.0–10.0 ng/ml).

In 4.2% of azoospermic patients elevated prolactin levels were found (49.4 ± 4.81 ng/ml: mean ± SEM). Another 27.4% had prolactin levels below the expected normal range of 3.5 ± 0.24 ng/ml mean ± SEM (normal range 5–20 ng/ml). Hormone levels in the fertile control group were FSH 9.9 ± 0.822 mIU/ml (mean ± SEM), LH 13.88 ± 2.72 mIU/ml (mean ± SEM), testosterone 9.50 ± 0.89 ng/ml (mean ± SEM) and prolactin 13.88 ± 1.88 ng/ml (mean ± SEM).

Cryptorchidism

In 33 azoospermic patients (9%), undescended testes were found (unilateral in 10 and bilateral in the rest).

Varicocele

Varicocele was diagnosed by the Valsalva manoeuvre in only 11 patients (2.9%).

Other conditions

Nine azoospermic patients had thickened epididymes and in 1 case nodules were palpable in the vas deferens.

The semen of 12 azoospermic patients exhibited non-liquefaction and in 1 patient excessive pus cells were found.

Another 24 azoospermic patients also complained of erectile dysfunction and 8 had high blood pressure; 1 azoospermic patient suffered a bullet wound injury to one testis and another had a previous hernia repair. Urogenital tuberculosis was suspected in 1 patient who presented with urethral stricture following a history of pulmonary TB.

Karyotype analysis in 12 azoospermic patients showed no abnormality.

Table 5 Comparison of Type of Azoospermia with Others Reported in the Literature

Reference	*Total with azoospermia*	*Type of azoospermia*		
		Obstructive (%)	*Testicular failure (%)*	*Other*
Franchimont *et al* (1972)	24	5 (21)	10 (42)	9
Hunter *et al* (1974)	20	7 (35)	13 (65)	—
Pryor (1983)	261	37 (14)	42 (16)	14
Girgis and Hafez (1977)	1057	587 (55)	444 (42)	24
Micic (1987)	225	104 (46)	31 (14)	90
Present findings	369	159 (43)	1515 (41)	59

Discussion

Much less is known about male than female infertility (Population Information Programme, 1983), partly because men are less likely to seek a full medical examination or treatment. Azoospermia is one of the most difficult conditions to manage. The high incidence of ablative testicular dysfunction and ductal occlusion in this series is suggestive of aetiology occurring either much earlier in reproductive development, or else patients present for medical advice when the condition is so far advanced that severe damage has been caused. The long cohabitation period noted in most patients before they seek treatment, combined with a history of multiple urogenital infection, supports this theory. The investigation of male infertility now comprises a range of methods that include hormone assays, testicular biopsy with staining technique, ultrastructure techniques and radiological methods. The high rate of reduced testicular volume could be indicative of previous urogenital infection, resulting in orchitis and subsequent shrinkage.

The causes of azoospermia include ductal obstruction from inflammatory, congenital and traumatic conditions as well as endocrine and primary testicular pathology. It was noted that 10% of all patients in the study were professional drivers. The testes are normally in an environment which is 2.2°C cooler than the intra-abdominal temperature, and it has been found that an increase in temperature suppresses spermatogenesis (Badenoch, 1945; Harrison and Winer, 1948; Waites, 1970). From this study it appears that professional driving associated with excessive cabin heat is associated with testicular damage.

Post-testicular ductal obstruction, found in a large number of patients, is a curable condition. Microsurgical excision of the obstruction with anastomosis has yielded good results. Derrick *et al.* (1973) reported a pregnancy rate of 19.5% in 1630 cases and Lee (1976) found a pregnancy rate of 35% in 181 cases. Wagenknecht (1982) had a tubal patency rate of 76% using various microsurgical techniques. Inflammatory occlusion usually occurs at the junction of the lower vas and the cauda of the epididymis. A differential diagnosis of obstruction (ejaculatory duct, vasal or epididymal) from primary testicular failure must be made. Of 453 patients with excretory azoospermia, Wagenknecht (1982) found 52% to have occlusion at the epididymo-vasal junction. In an analysis of 1294 childless males, Amelar and Dubin (1978) found vasal obstruction in 7.4%. A WHO multicentre study of 7273 couples (Comhaire *et al.*, 1987) presented 58 patients with obstructive azoospermia following a median duration of infertility of 3 years.

Previous labour migration policies, the impact of urbanisation, history of poor health care, delay in seeking treatment and social conditions could account for a history of single and multiple medical problems in the majority of our patients.

The hormonal studies (LH, FSH and testosterone) confirmed expected diagnostic findings with ductal obstruction and testicular damage. Since the majority of patients in the present study were not keen on either artificial insemination or adoption, it will be difficult to find a solution to this major problem.

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Responses of Erectile Tissue from Impotent Men to Pharmacological Agents

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Summary—Erectile tissue was removed from the corpora cavernosa of 25 impotent men undergoing surgery for insertion of penile prostheses. Strips, set up in an organ bath, were contracted by the alpha-adrenergic agonist phenylephrine. There was no significant difference between tissue taken from men with diabetes, alcoholism, Peyronie's disease or men with no obvious condition causing the impotence. The sensitivity of tissues from hypertensive patients was significantly reduced but this was probably due to drugs being taken for hypertension. Precontracted tissues could be relaxed by acetylcholine or isoprenaline. The responses, however, were inconsistent, so that no difference between the different groups of patients was apparent.

Penile erection and detumescence result from specific vasodilatation and constriction which changes the blood flow through the erectile bodies of the penis (Andersson *et al.*, 1984; Carati *et al.*, 1987). This is controlled by activity of the parasympathetic and sympathetic nerves and therefore depends on the integrity of the autonomic nerves to the penis and on the blood supply. The role of the smooth muscle cells within the corpus cavernosum is not clear but they probably also modify the blood flow through this body, since the smooth muscle has a similar innervation to that of blood vessels (McConnell *et al.*, 1979; Polak *et al.*, 1981). The responsiveness of the smooth muscle to putative neurotransmitters may therefore be a good indication of the microvascular pathology of the penis.

The occurrence of impotence has been associated with a number of clinical conditions including diabetes, alcoholism, Peyronie's disease and vascular disease (Smith, 1981). This could result from changes in the nervous or vascular systems. There is some evidence for a reduction in the nerves to the penis of patients with diabetes compared with "non-neuropathic" impotent men (Melman *et al.*, 1980; Lincoln *et al.*, 1987) but no reports have been published on the contractility of erectile tissue. In the present study, penile tissue was obtained from the corpora cavernosa of 25 patients undergoing surgery for insertion of penile prostheses. The purpose of the study was to see if the contractile response to the alpha-adrenergic agonist, phenylephrine, varied according to the clinical condition associated with impotence.

Material and Methods

Human erectile tissue was removed from the corpora cavernosa of patients undergoing surgery for insertion of penile prostheses. The patients were premedicated with pethidine (100 mg) and atropine (0.06 mg). The tissue was placed in modified Krebs solution and either used within 3 h or stored overnight at 5°C. Results were unchanged by the cold storage. Connective tissue was carefully removed and 2 strips 15 × 2 mm prepared. These were mounted under 0.5 g tension in an organ bath at 37°C and allowed to equilibrate in Krebs solution for 1 h. The contractile effect of phenylephrine (PhE) was then measured with a force transducer by cumulative addition of increasing doses to give concentrations in the bath from 10^{-8} to 10^{-4} M. The relaxant effects of acetylcholine or isoprenaline were measured in some strips after they had been contracted with PhE at a dose that was one-third of

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that which induced the maximum contraction (usually 3×5^{-5} M).

Modified Krebs had the following composition (mM): NaCl 120, KCl 5.0, $CaCl_2$ 2.5, $MgSO_4$ 1.0, NaH_2PO_4 1.0, $NaHCO_3$ 25.0 and glucose 11.0 equilibrated with 5% CO_2 in O_2. Drugs used were phenylephrine hydrochloride (Sigma), acetylcholine chloride (Hopkins and Wilkins) and isoprenaline sulphate (Sigma).

The responses of the strips from each patient were averaged and the ED_{50} calculated from the dose response curve. The mean ED_{50}s for each group were compared with Student's *t* test. There was no significant difference in the slopes of the individual dose response curves.

Results

When tissues were first set up in the organ bath they had no spontaneous activity, but during the course of the experiment spontaneous contractions of 1 to 2 g often occurred at the rate of 0.1 to 2.0/min. The threshold for contraction to PhE was about 10^{-8} M for all tissues that responded. The contraction developed slowly but was well maintained once it reached a plateau at 2 to 4 min. Maximum contraction of 1 to 4 g occurred with PhE at 3×10^{-5} M in most tissues but in a few, especially those from hypertensive patients, higher concentrations were necessary. The ED_{50} was calculated for tissues obtained from each patient.

The Table shows ED_{50} values obtained for 25 patients and 2 organ donors together with the age, clinical condition and drugs being taken before surgery. Mean dose response curves have been plotted for diabetic (n = 5) and hypertensive (n = 4) patients (Fig. 1). As no controls were available from normal men, the mean values from 2 kidney donors and from 4 patients with no obvious condition associated with impotence have also been plotted. There was no significant difference between the tissues from diabetics and this last group ($P > 5\%$). The kidney donors were much younger than the other patients and had both received multiple medication before death. This may explain the shift to the right of the dose response curves.

Table Summary of Clinical Details and Response to Phenylephrine of Erectile Tissue from 25 Impotent Men and 2 Kidney Donors

No	*Age (years)*	*PhE ED50 (M)*	*Clinical details*	*Recent drug history*
1	52	1.42 × 10−6	Diabetes	Insulin
2	64	2.15 × 10−6	Diabetes	Glibenclamine
3	57	1.07 × 10−6	Diabetes	Oral diabetic drug
4	74	1.45 × 10−7	Diabetes	Glibenclamine
5	53	2.92 × 10−7	Diabetes	Insulin
6	71	2.30 × 10−5	Hypertension	Ameth-DOPA
7	59	no response	Hypertension	Stilboestrol
8	69	8.46 × 10−6	Hypertension	Pindolol, *etc*
9	61	1.37 × 10−5	Aortic bypass	Captopril, *etc*
10	64	no response	Hypertension	Nil
11	64	7.03 × 10−6	Hypertension	Prazosin + metaprolol
12	50	4.03 × 10−7	Alcoholic	Indomethacin
13	48	4.9 × 10−6	Alcoholic	Indomethacin, *etc*
14	55	3.06 × 10−7	Peyronie's	Nil
15	62	9.78 × 10−7	Peyronie's	Nil
16	60	3.20 × 10−6	D + A + H	Nil
17	51	1.45 × 10−7	Depression	Nil
18	71	1.00 × 10−5	Periph. neurop.	Allopurinol
19	40	4.12 × 10−6	Depression	Allopurinol + testosterone
20	67	3.58 × 10−7	Prostatectomy	Sedatives
21	66	1.50 × 10−6	Urethoctomy	Antibiotics
22	51	1.80 × 10−6	Emphysema	Indomethacin
23	57	8.50 × 10−7	None obvious	Nil
24	63	2.98 × 10−7	None obvious	Indomethacin
25	57	5.39 × 10−7	None obvious	Nil
26	18	1.86 × 10−6	Kidney donor	Many
27	16	1.52 × 10−6	Kidney donor	Many

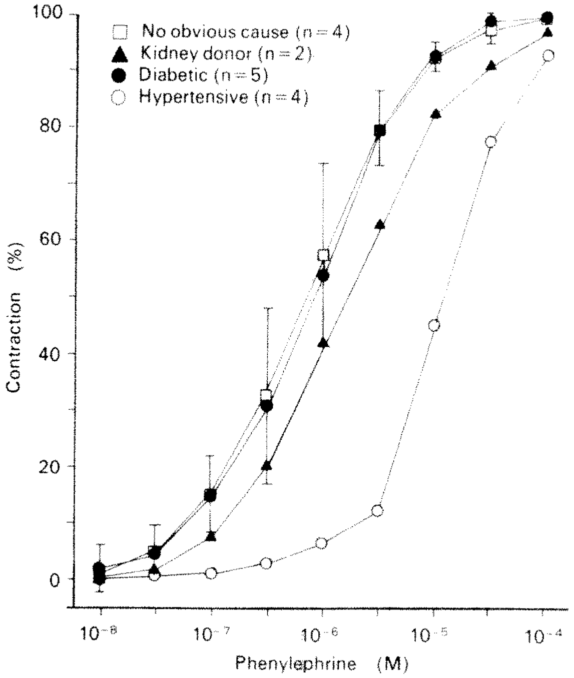

Fig. 1 Contractile responses to phenylephrine of strips of erectile tissue from the corpora cavernosa of impotent men and kidney donors. Each point represents the mean of several tissues as indicated. Standard deviations are shown for the tissues from patients with no obvious condition associated with impotence (□).

The tissue from the hypertensive patients, most of whom were taking drugs that influence the autonomic nervous system, was significantly less sensitive to PhE.

The responses of the tissues from the 2 patients with Peyronie's disease and the 2 who had urethral surgery all lay within the range for the diabetic and "control" values, whereas those from the 2 alcoholic and 3 neurological patients showed much greater variability.

The addition of acetylcholine (ACh) and isoprenaline (Isop) produced relaxation of the precontracted tissue. However, the relaxation was very variable and was difficult to relate to the clinical condition (Fig. 2). Particularly for ACh, the relaxation was rarely more than 50% and in some cases did not fall below 80% of the precontracted value. Furthermore, the relaxation was poorly maintained, so that the tissue was often more contracted with higher doses. It was not possible to obtain ED_{50} values or compare different tissues satisfactorily.

Discussion

It is generally considered that relaxation of the erectile tissues is associated with erection, whereas contraction occurs when the penis is flaccid (Langley and Anderson, 1895; Dorr and Brody, 1967). The contraction is produced by the release of noradrenaline from sympathetic nerve fibres, which acts on alpha-adrenoceptors on the arterioles and on the erectile tissue in the sinusoidal spaces. In the present experiments there was complete overlap of ED_{50} values to phenylephrine for tissues from patients with diabetes, Peyronie's disease, no obvious condition causing impotence and following urethral surgery. However, there was a significant difference between these and tissues from kidney donors and hypertensive patients, where the dose response curves were moved to the right. This difference can be explained by drugs being taken before removal of the tissue. The kidney donors were also much younger than the older patients and may not therefore be strictly comparable. It is of interest that the tissues from diabetics were not significantly different from those of non-diabetic men, since Lincoln *et al.* (1987) and Melman *et al.* (1980) reported that the noradrenaline content of the corpus cavernosum from diabetic patients was significantly lower than that from other impotent patients. Dose response curves from corpus cavernosal tissue removed during penile amputation were also shifted to the right compared with those found in the present study (mean ED_{50} approximately 8×10^{-6} M $n=9$, calculated from Adaikan and Karim (1981)), but most of these patients had been taking oestrogens for several months and the tissues were therefore not equivalent to those in the present series.

The neurotransmitter responsible for erection has yet to be determined. Although acetylcholine and the beta-adrenergic agonist isoprenaline produced relaxation, there is evidence from the use of blocking agents that erection is due to activity of non-cholinergic, non-adrenergic fibres (Wagner and Brindley, 1980; Carati *et al.*, 1987). Furthermore, the patients in the present study were given atropine before surgery. It is perhaps not surprising, therefore, that inconsistent responses were obtained to acetylcholine and isoprenaline. It should be noted that Lincoln *et al.* (1987) found a reduction in acetylcholine esterase positive nerves in 3 of 5 diabetics compared with patients in other groups.

The present results suggest that, even if these are not the neurotransmitters involved, at least some of the apparatus producing erection is intact in

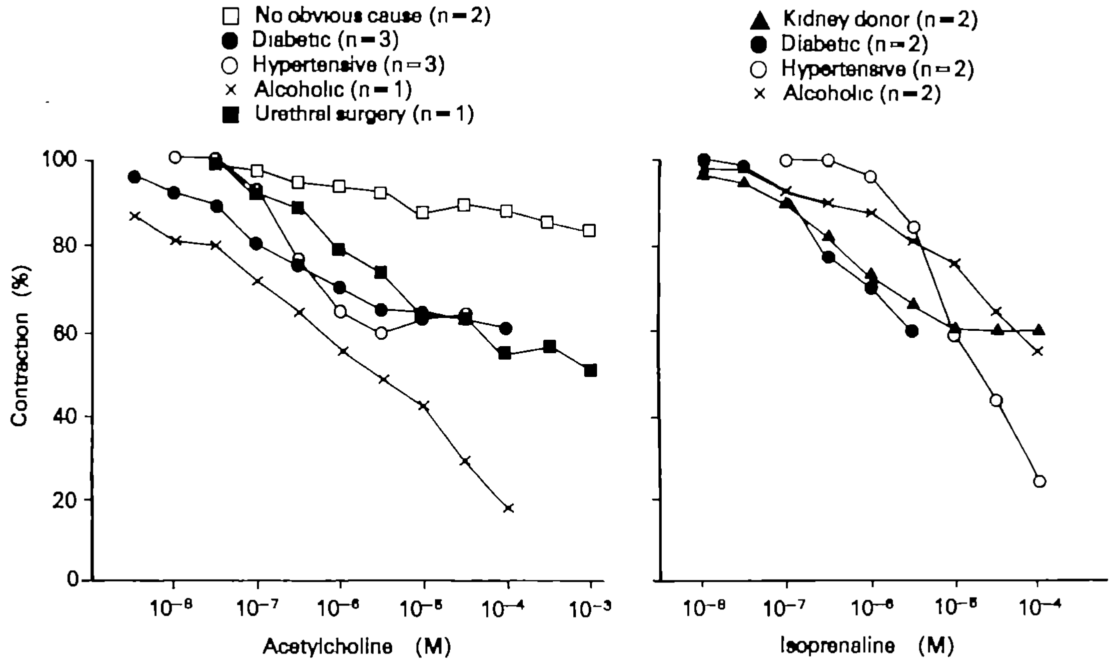

Fig. 2 Relaxation of erectile tissues from impotent patients The tissues were pre-contracted with 3×10^{-5} M phenylephrine, acetylcholine or isoprenaline was then added cumulatively

impotent men and that the inhibitory effects of the sympathetic neurotransmitter are normal. Furthermore, there were no obvious differences between groups. It is unfortunate that it is not possible to compare these results with those from normal potent men. However, it seems probable that the impotence may have arisen mainly from deterioration of the nerve supply rather than the vascular system.

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Duplex Scanning in Suspected Vasculogenic Impotence: a Worthwhile Exercise?

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Summary—The value of duplex scanning in the assessment of impotence was evaluated in 146 impotent men. Scanning was by means of a Diasonics DRF 400 and penile artery measurements were taken before and after the intracorporeal injection of papaverine hydrochloride. The penile/brachial index was measured in 82 patients and its predictive value compared with the results of duplex scanning and papaverine-induced erection. On scanning evidence of good arterial inflow but poor erections, indirect evidence of venous leakage was assumed.

The results showed that the deep artery responses best charaterised the erectile response, with the dorsal artery being less helpful.

All 37 patients with full erections following papaverine exhibited bilateral deep artery peak velocities of $\geqslant 25$ cm/s. Of the remaining 109 sub-optimal responders, 17 also has this finding; all had undergone dynamic cavernosography, with 16 exhibiting venous leakage.

The penile/brachial index was found to classify 13 patients incorrectly.

A critical value of deep artery response to attain erection is postulated, enabling more logical use of cavernosography. The penile/brachial index was shown to be suspect and it was concluded that duplex scanning is a useful, non-invasive method in the assessment of impotence.

Arterial insufficiency is a well recognised cause of erectile dysfunction (Michal, 1982; Virag *et al.*, 1985). The objective non-invasive assessment of penile artery blood flow still relies to a great extent on measures based upon the penile blood pressure, such as the penile/brachial index (PBI) (Kempczinski, 1979). The reliability of the PBI has been questioned and although highly sensitive in diagnosing penile vascular deficit at values below 0.6, it cannot exclude it (Metz and Bengtsson, 1981). This fact is not surprising, since studies on which of the penile arteries are interrogated during continuous wave doppler studies have concluded that only the dorsal is reliably measured (Casey, 1980; Reiss, 1985).

The advent of the duplex scanner allows reliable visualisation of the penile vessles; together with the intracavernosal injection of papaverine, this has facilitated a dynamic assessment of the penile vascular reaction during erection (Lue *et al.*, 1985; Robinson *et al.*, 1987).

The contribution of venous leakage in impotence is also unclear. It has been suggested that duplex evidence of good cavernosal artery flow, in conjunction with poor clinical erection, would allow a more selective application of dynamic cavernosography (Mueller and Lue, 1988).

Patients and Methods

The series comprised 146 impotent men (age range 19–74 years, mean 47) of various clinical aetiologies (Fig. 1).

All patients underwent duplex scanning of the dorsal and deep penile arteries both before and after the intracorporeal injection of 60 mg papaverine hydrochloride. The duplex scanner allowed direct interrogation of the individual penile vessels, with the measurement of peak blood velocity in

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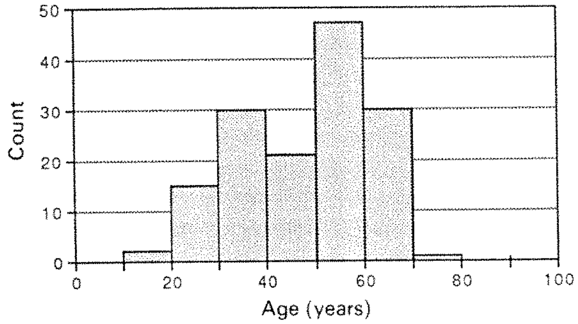
Read at the 44th Annual Meeting of the British Association of Urological Surgeons in Buxton, June 1988



Clinical Aetiology	No.
Diabetes	51
Spinal injury	25
MS	10
TURP	10
Pelvic fracture	6
Psychological	5
Miscellaneous (vascular disease, pelvic surgery, Peyronies)	39
Total	146

Fig. 1 Patient population.

both the dorsal and deep arteries and internal diameter measurement of the deep arteries. Following injection, the patients stood for 2 min and scanning was then repeated within the next 5 min. Flow parameters were again recorded and any subsequent erection clinically graded.

The penile systolic pressure was determined in the supine position in 82 patients using an 8.5 MHz continuous wave pencil probe, with a 2.5 cm digital pressure cuff at the base of the penis. Comparison with the brachial pressure using the same probe allowed the PBI to be calculated.

Seventeen patients underwent dynamic cavernosography. Cannulation of the corpora cavernosa allowed measurement of the flow of normal saline required to attain and maintain an erection following the injection of 60 mg papaverine. Simultaneous recording of intracavernosal pressure was also undertaken. Saline infusion was commenced 5 min following papaverine injection, at an initial rate of 26 ml/min.

This was increased in a stepwise fashion until either the intracorporeal pressure had stabilised for 2 min or an erection had been achieved. A maximum rate of 160 ml/min was used. Infusion was slowed to a maintenance value if an erection was achieved, keeping the corporeal pressure above 90 mmHg. Contrast media were then infused (60% Omnipaque diluted 1:1 with normal saline) at the maintenance value during full erection, or at maximal flow rate if rigidity was sub-optimal. X-ray screening optimised the identification of any abnormal venous channels, with 3 X-ray pictures (one A-P, right and left oblique) being taken for reference.

Results

The anatomy of the penis was well seen, with single deep arteries showing at the base (Fig. 2). The clinical response to papaverine is shown in Table 1.

Statistical analysis (unpaired *t* test for parametric and Man Whitney U test for non-parametric data)

Table 1 Post-papaverine Response

*Erection grade**	*No. of patients*
0	3
1	29
2	77 (includes 17 with suspected venous leakage)
3	37 (all with bilateral peak deep artery velocities $\geqslant 25$ cm/s)

* 0 = No reaction.
1 = Tumescence but no rigidity.
2 = Sub-optimal rigidity.
3 = Full erection.

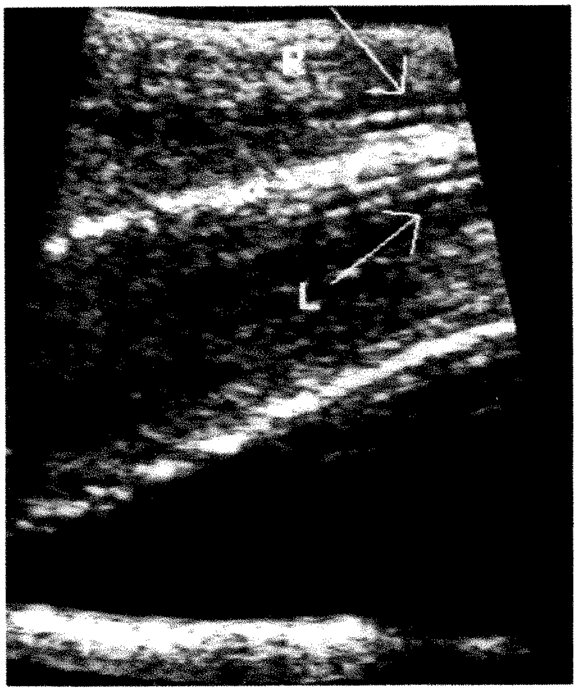


Fig. 2 Longitudinal real time scan of penis showing deep arteries (arrowed) and intercavernosal septum.

Table 2 Analysis of Response Parameters*
(A) Penile artery peak velocity changes following papaverine (mean ± SD)

	Arterial response (cm/s)			
Erection grade	*Dorsal increase*	*Dorsal total*	*Deep increase*	*Deep total*
0 (n = 3)	4 ± 6.9	4 ± 6.9	23 ± 4.3	23 ± 4.3
1 (n = 29)	23.7 ± 27	36.1 ± 33	30.6 ± 11.2	33.5 ± 10.5
2 (n = 61)	30.8 ± 26	47.3 ± 32.2	32.4 ± 12.3	41.4 ± 12.6
3 (n = 37)	33.1 ± 29.1	64.3 ± 34.5	68.9 ± 30.7	87.2 ± 31.5
Statistical analysis				
1 *v* 2	ns	ns	ns	$P = 0.004$
2 *v* 3	ns	ns	$P < 0.0001$	$P < 0.0001$
3 *v* 1	ns	$P = 0.001$	$P < 0.0001$	$P < 0.0001$

* For the purposes of analysis those patients with venous leakage have been excluded.

(B) Deep artery diameter increase following papaverine

Erection grade	*Diameter increase (%)*
0 (n = 3)	26.6 ± 46.1
1 (n = 29)	37.6 ± 27.5
2 (n = 61)	42.4 ± 23
3 (n = 37)	64.6 ± 32.2
Statistical analysis	
1 *v* 2	ns
2 *v* 3	$P = 0.001$
1 *v* 3	$P = 0.001$

ns = Not significant at 5% level.

of the dorsal and deep artery response parameters following papaverine showed that the deep artery changes best corresponded with erectile function (Table 2).

All 37 patients who obtained a good erection exhibited bilateral peak deep artery velocities of at least 25 cm/s, with significant differences in deep artery diameter increases between sub-optimal and good clinical responders (Table 3).

Of the 109 patients with sub-optimal erections, 17 had this critical deep artery velocity, with all undergoing dynamic cavernosography. A further 3 patients with duplex evidence of an arterial inflow deficit, but clinical histories suggestive of venous leakage, also had this procedure and acted as controls (Table 3).

Of the 17 patients with suspected venous leakage, 16 showed flow, pressure and X-ray criteria of venous leakage (Fig. 3). In the remaining patient no leakage was demonstrated and this cannot be explained. The 3 control patients all showed low flow rates to attain and maintain an erection with no leakage on X-ray.

Of the patients with proven leakage, 4 have undergone surgical venous ligation; 2 have regained spontaneous erections sufficient for intercourse, 1

Table 3 Results of Dynamic Cavernosography

Venous leakage proven

No. of patients	*Flow rates (ml/min)* *Obtain erection*	*Maintain erection*	*ICP (mmHg)*
13	Mean 71.3 (40–141)*	Mean 45.6 (11.5–80)*	94–150
3	Unable to obtain at rate of 160 ml/min		35–51
No leak seen			
1	26	3.9	113
Control patients			
3	Mean 35 (26–53)*	Mean 15 (10–15)*	150

ICP = Maximum intracavernosal pressure achieved.
* Value ranges.

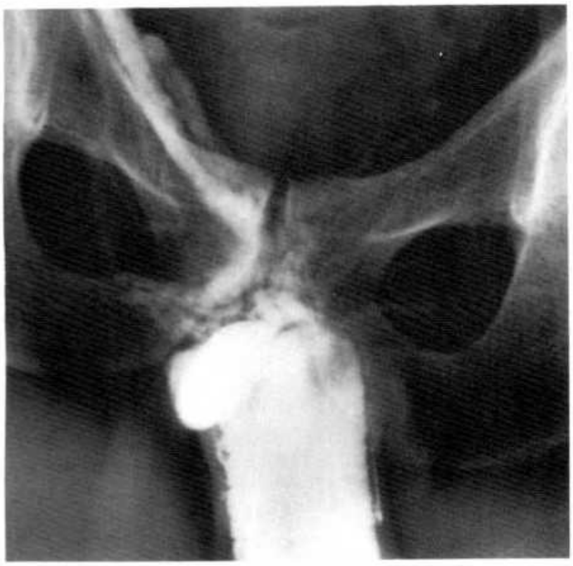


Fig. 3 A-P film of dynamic cavernosography showing leakage into pelvic veins.

still requires papaverine for a satisfactory response and 1, although having a good initial result, has now relapsed.

Since measurement of the PBI is often quoted as having included cavernosal artery readings (Goldstein *et al.*, 1982), the deep artery flow in the flaccid penis was investigated. The results showed that although a greater percentage of those obtaining good (25 cm/s) deep artery peak velocities had flow in 1 or 2 deep arteries in the flaccid state, a significant number (16.9%) did not (Table 4). In 50 patients (34%) no deep artery flow was demonstrable.

Four patients with proven venous leakage had PBI readings of <0.6; 4 patients with good deep artery flow rates and corresponding erections had a PBI below 0.9, but 5 patients with a PBI greater than 0.9 had poor erections and low deep artery readings. Thus the PBI was found to have a false classification rate of 15.8%.

Table 4 Flaccid Deep Artery Flow

Penile reaction	*No. of deep arteries detected*		
	0	1	2
0 (n=3)	3		
1 (n=29)	17	8	4
2 (n=61)	21	19	21
3 (n=37)	4	10	23
Venous leaks (n=16)	5	3	8

A sustained erection (>4 h) developed in 6 patients (4%). Resolution followed simple aspiration.

Discussion

This study demonstrates the fundamental role that deep artery function plays in erectile physiology. The results indicate that the peak deep artery velocity is a useful indicator of erectile function and that a critical value of this is required. Determination of this value has been shown to be a useful screening measure for suspected venous leakage. Venous leakage was found in approximately 10% of patients in this series. A much higher rate is quoted in series where our selection criteria for cavernosography were not used (Delcour *et al.*, 1984).

The injection of papaverine prior to dynamic cavernosography has been shown to reduce the flow needed to attain and maintain an erection, while increasing the intracavernosal pressure for a given flow rate (Lue *et al.*, 1986). This is due to the activation of a venous trapping mechanism, the exact nature of which is unclear, but which is required for erection and is also activated by cavernosal nerve stimulation (Juenemann *et al.*, 1986).

Studies of dynamic cavernosography without papaverine in normal subjects usually cite a flow rate of 80 to 120 ml/min to produce an erection, with maintenance values around 20 to 40 ml/min (Wespes and Schulman, 1984). The results in the small number of controls in this study demonstrate the much reduced flow rates needed, which may be important in patients with compromised cardiovascular reserve.

There are as yet few studies defining the normal values for cavernosography performed in conjunction with vasoactive drugs, but the finding of reduced flow rates has been confirmed (Wespes *et al.*, 1986). The effect of drug washout has not been studied but this method of venous assessment would appear to be more physiological.

Dynamic cavernosography was performed only in those patients with good arterial inflow. It has been suggested that compromised arterial inflow may be responsible for poor venous tone (Bookstein *et al.*, 1987). The results of venous surgery are only acceptable, however, in patients with normal arterial inflow (Wespes and Schulman, 1985).

The poor predictive value of the PBI is not suprising, since a continuous wave doppler picks up all signals in its path. Most PBI data must therefore be derived from dorsal artery readings, which carry the highest flow in the flaccid state.

The placing of a cuff at the base of the penis may distort readings due to an inappropriate fit, and also it may only be at the base that the deep arteries are single prior to branching. A distally placed pencil probe is thus prone to error, which the duplex transducer is not.

The duplex scanner is an expensive item but this should be viewed in relation to its multidisciplinary cardiovascular and gynaecological applications.

It is concluded that duplex scanning is the only reliable non-invasive method for the direct assessment of the penile vascular reaction during erection. The PBI is open to both conceptual and experimental errors, but until duplex instrumentation becomes less expensive it will continue to be used.

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Case Reports

Acute Scrotum due to Tick Bite

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Case Report

A 5-year-old boy presented with pain in the right hemiscrotum. On examination, the right hemiscrotum was swollen to about twice the normal size, was tender and had a circular erythematous zone with a central black spot. The testis, epididymis and the cord were not palpable, making the exclusion of testicular torsion difficult. Upon more careful examination, using magnification, the black spot was seen to be protruding a few mm from the skin, giving the impression of a foreign body. Using a mosquito clamp, the foreign body was extracted and examined in detail under the microscope, revealing a tick belonging to the family *Ixodoidae* As the tick was in the larval stage, identification of the genus was not possible.

The patient was given cefadroxil 200 mg 3 times daily and naproxen, a non-steroidal anti-inflammatory drug, 125 mg twice daily. The patient was seen again 7 days later. This time a small infiltrated pink nodule was found, it measured 0.5 cm and was diagnosed as a granuloma and treated with triamcinolone acetonide cream twice daily (Goldman, 1963).

Comment

Larvae, nymph and adult ticks attack any available animal, including man, and remain attached for several days, causing local reactions that include itching, urticarial swelling and haemorrhage of the skin. Possible systemic manifestations caused by the salivary toxins are pyrexia and acute ascending flaccid paralysis (Marshall, 1967). Ticks also convey many infectious diseases (Rees and King, 1987).

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Near-fatal Urinary Peritonitis Secondary to Ureteric Calculus

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Case Report

A 35-year-old man was admitted urgently with severe right loin colic and haematuria. A 5-mm calculus lying over the right sacroiliac joint was confirmed radiologically He was given pethidine and encouraged to drink clear fluids. Over the next 24 h the pain became constant and localised in the right iliac fossa. Abdominal distension, diffuse peritonitis and hypotensive shock supervened.

At emergency laparotomy 1.5 litres of offensive urine were found intraperitoneally. The peritoneum lateral to the ascending colon had perforated and urine was discharging from a grossly distended renal pelvis. The ureteric calculus was dislodged into the renal pelvis and removed. The renal pelvis was drained extraperitoneally and the abdomen closed following copious peritoneal lavage with 1 g tetracycline dissolved in 1 litre of normal saline.

Post-operatively the patient was treated with intravenous ampicillin 500 mg *tds* for *Escherichia coli* bacteraemic shock and was discharged home on day 22.

Comment

Most ureteric calculi under 5 mm in diameter pass spontaneously and are treated conservatively. Complications usually consist of infection in the short term and deterioration in renal function in the long term (Whitaker, 1986).

Although urinary extravasation is well documented in ureteric obstruction secondary to calculus, an intraperitoneal collection of this magnitude is rare (Hindmarsh, 1984). Urinary peritonitis carries a high mortality rate and early recognition and prompt surgical intervention are imperative.

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Primary Hodgkin's Disease of the Urinary Bladder

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Case Report

A 54-year-old man taking warfarin because of transient ischaemic attacks developed microscopic haematuria which persisted despite stopping the warfarin. An intravenous urogram showed a filling defect in the right side of the bladder. At cystoscopy a 5-cm solid tumour was found and resected endoscopically. Histologically it was mixed cellularity Hodgkin's lymphoma.

Computed axial tomography showed no evidence of extension into the pelvis. The liver and spleen were normal and neither pelvic nor intra-abdominal lymphadenopathy was detected. Chest X-ray, full blood count, liver function tests and bone marrow aspiration were normal.

External beam radiotherapy using an 8 MeV linear accelerator was commenced with parallel opposed fields: 3500 cGy to the lower abdomen and pelvis in 20 fractions over 4 weeks followed by 1000 cGy to the bladder in 5 daily fractions. Cystoscopy a year later showed no tumour and he remains well 3 years later.

Comment

Primary lymphoma of the urinary bladder is rare (Aigen and Phillips, 1986) and a search of the literature found only 1 patient with Hodgkin's lymphoma (Marconis, 1959), who survived for at least 16 months after a cystectomy.

This seems to be only the second reported case of primary Hodgkin's disease of the urinary bladder and the first reported case treated successfully with radiotherapy.

Acknowledgement

I thank Mr K. C. Vaughton for allowing me to report this case.

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Piroxicam-induced Renal Failure following Relief of Chronic Retention

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Case Report

A 76-year-old man presented with acute on chronic retention. He was a diet-controlled diabetic, osteoarthritic and hypertensive, taking piroxicam and polythiazide. He had a bladder palpable to the umbilicus and a large irregular prostate. Serum chemistry on admission was: Na 134 mmol/l, K 7.4 mmol/l, creatinine 1857 mmol/l, urea 77 mmol/l.

He was catheterised and over the following 3 days had a diuresis of 28 litres; creatinine fell to 592, urea to 16.6 and K to 3.5. Fluid replacement was adequately maintained over the first 2 days but on the third day he became clinically dehydrated for approximately 12 h, although his blood pressure was maintained. Despite rehydration, on the fourth day he became oliguric, developed oedema, a raised JVP and bilateral basal crackles. There was no response to osmotic or thiazide diuretics. His urea and creatinine climbed to 29.2 and 925 mmol/l respectively. Creatinine clearance was 0.11 ml/s. Non-steroidal anti-inflammatory drug (NSAID)-induced renal insufficiency was suspected and piroxicam was withdrawn. Three days after stopping the drug, the urinary output improved and the oedema resolved. Two weeks following admission the serum chemistry had returned to normal. He subsequently underwent a successful transurethral prostatectomy.

Comment

Reversible renal insufficiency is a well recognised side effect of NSAIDs (Clive and Stoff, 1984).

Vasodilator prostaglandins PGE2 and PGI2, synthesised in the kidney in response to vasoconstrictors such as angiotensin II and ADH, maintain renal blood flow in times of circulatory insufficiency. NSAIDs (of which piroxicam is one) inhibit the enzyme cyclo-oxygenase and thereby block the conversion of arachidonic acid to endoperoxides, the precursors of PGE2 and PGI2. In hypovolaemia, a relative deficiency of these renal vasodilators leads to inadequate renal perfusion and subsequent renal insufficiency, probably caused by ischaemic damage (Weisman *et al.*, 1985; Unsworth *et al.*, 1987).

Our patient had contributory factors that predisposed to NSAID-related renal failure. He was diabetic and mildly hypertensive and took diuretics. Diuretics activate the renin-angiotensin system and create a dependence on the vasodilator prostaglandins to maintain renal perfusion. In addition, he probably became hypovolaemic following a profound diuresis.

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Rhabdoid Tumours of the Spermatic Cord

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Rhabdoid tumour is a clinically rare and aggressive neoplasm that was initially described as a variant of Wilms' tumour.

Case Report

K.A., a 3-month-old boy, was admitted in August 1987 with a 1-month history of scrotal swelling. Three tumours, each about 5 × 4 mm, could be palpated at the left spermatic cord and another tumour measuring 2 × 2 mm was found at the right spermatic cord. Chest X-ray, routine blood analysis and bone marrow smear were normal. Blood chemistry laboratory examinations were within normal limits except for a high level of LDH (1025 u/l).

Under light microscopy, almost all cells contained amphophilic cytoplasm. Many contained orange-red, round, hyaline-like, slightly PAS stain positive inclusions (Fig. 1).

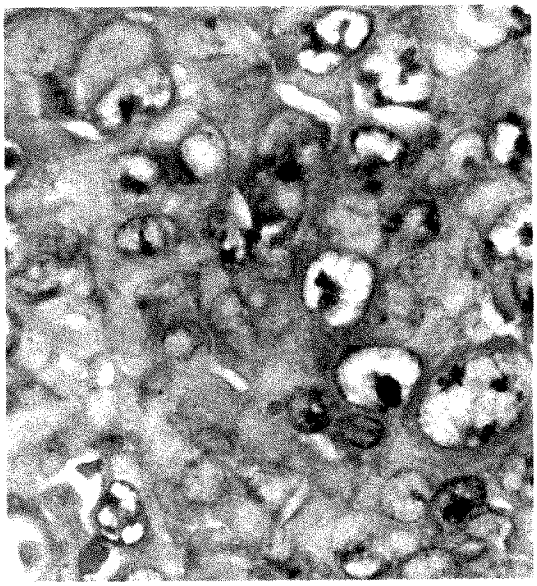

Fig. 1 Many tumour cells contain amphophilic cytoplasm with hyaline-like inclusions. (H and E × 400).

Under electron microscopy, most conspicuous was a background of scattered bundles of filaments, each filament measuring 10 nm in diameter (Fig. 2). Immunohistologically, the reactions for desmin, vimentin and cytokeratin were positive. Results from staining for myoglobin, neurofilament, S-100 protein and α1 antichymotrypsin were negative. Samples from dissected lymph nodes showed clear evidence of metastasis and the patient underwent chemotherapy (vincristine, actinomycin D and cyclophosphamide). Five months after surgery we could find no further metastasis.

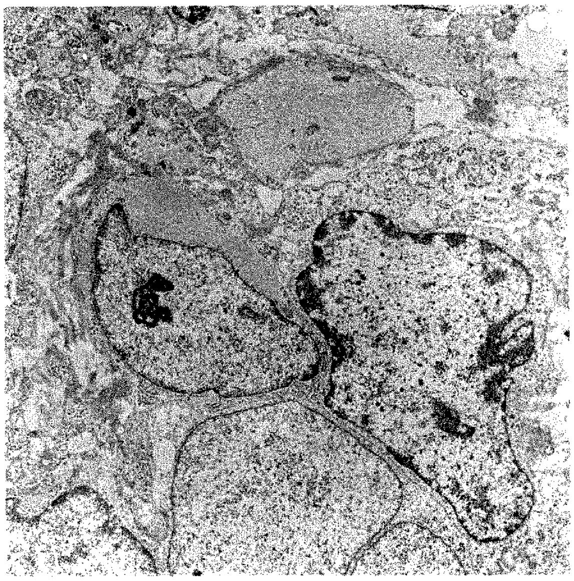

Fig. 2 Tumour cells with nuclei varying from round to oval, with large nucleoli. (× 1620).

Comment

Theories concerning the histogenesis of this tumour vary considerably. Some authors think it originates from the neural crest or histiocytes; others have suggested an epithelial derivation. Immunohistologically, a rhabdoid tumour shows negative on desmin staining but in the present case it was positive.

We used an anti-cancer chemotherapy regimen usually applied to rhabdomyosarcoma and have prevented any tumour recurrence or metastasis for 5 months.

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An Unusual Case of Rectovesical Fistula

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Case Report

A 57-year-old market gardener presented with painless haematuria. Investigation revealed a duplex right kidney and a urachal carcinoma arising from the bladder vault. This was treated initially by transurethral resection and radiotherapy. Partial cystectomy with *en bloc* resection of the midline peritoneum and extraperitoneal fat was subsequently performed for local recurrence.

Ten years later he developed frequency and pneumaturia. Cystoscopy revealed a tiny scarred bladder and a large fistula into the rectum; sigmoidoscopy demonstrated the fistula 8 cm from the anus; biopsies showed severe radiation damage.

At laparotomy the bladder was scarred and shrunken without obvious tumour. The rectum was resected and a colo-anal anastomosis fashioned. The 3 ureters were diverted into an ileal loop.

Comment

Urachal carcimona accounts for less than 1% of malignant bladder tumours and the outlook is poor (Lane, 1975). Some believe that partial cystectomy with *en bloc* excision of tissues to the umbilicus can produce adequate clearance in selected patients, whereas others regard radical cystectomy as mandatory (Johnson *et al.*, 1985).

Bladder tumours cause less than 5% of fistulae between large bowel and bladder—the majority are due to diverticular disease; pelvic irradiation accounts for 3% (Pollard *et al.*, 1987). Most involve the sigmoid colon and invariably when the rectum is involved, the cause is malignant disease or radiotherapy.

In this case the grossly diseased bladder made any attempt to retain bladder function inappropriate. Diversion of both urinary and faecal streams would mean life with two permanent stomas, and urinary diversion into the colon would have resulted in both a "wet colostomy" and metabolic problems. For these reasons urinary diversion with colo-anal anastomosis was undertaken.

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Angiosarcoma of the Penis

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Case Report

A 57-year-old Caucasian male presented with a 3-month history of a red nodule on the dorsum of the penis, in the coronal sulcus, causing pain on erection. He was otherwise well and asymptomatic. There was no history of exposure to thorium-containing X-ray contrast media or polyvinyl chloride fumes. On examination a cystic red nodule measuring 1 × 1 cm was present on the penis; further physical examination was normal. A local excision of the nodule was performed.

Histological examination revealed that the nodule was composed of large pale eosinophilic cells with large hyperchromatic nuclei and prominent nucleoli. Cytoplasmic boundaries were indistinct. In areas where cells were more tightly packed they had a fusiform appearance.

Free red cells together with haemosiderin pigment were present. Multiple vascular channels crossed the mass, lined by highly atypical endothelial cells. Mitoses were not seen. Immunohistochemical stains for Factor VIII antigen were strongly positive, especially in cells around the lumina, confirming the endothelial nature of the tumour (Fig.). No evidence of cutaneous tissue was seen. A diagnosis of angiosarcoma arising from the corpora cavernosa was made. This was followed by a wider excision of the site of the nodule, histology of which revealed only preputial skin with no evidence of residual tumour. Post-operative recovery on both occasions was uneventful. The patient has now been followed up for a year with no sign of recurrence of the tumour or the appearance of metastases.

Comment

Malignant neoplasms of the penis are rare, accounting for 0.5 to 1.5% of malignancies in males and causing 122 deaths in 1984 in England and Wales. The most common cancer arises from the squamous epithelium and soft tissue tumours are uncommon. In a review of 46 soft penile tissue lesions by Dehner and Smith (1970), 41% were angiomatous in origin; these included 7 malignant tumours, 3 of which were angiosarcomas; the remainder were Kaposi's sarcomas. Since 1883 there have been 35 possible cases of penile angiosarcoma (Creile, 1905; Waugh, 1952; Dehner and Smith, 1970; Deutsch *et al.*, 1973; Ghandur-Mnaymneh and Gonzalez, 1981; Wasmer *et al.*, 1981), but 1 of these patients was reported twice. Two tumours were reported in infants but the cell of origin of these growths is uncertain. Ours is the first report of such a tumour in the UK and of factor VIII antigen immunohistochemical staining in a penile angiosarcoma.

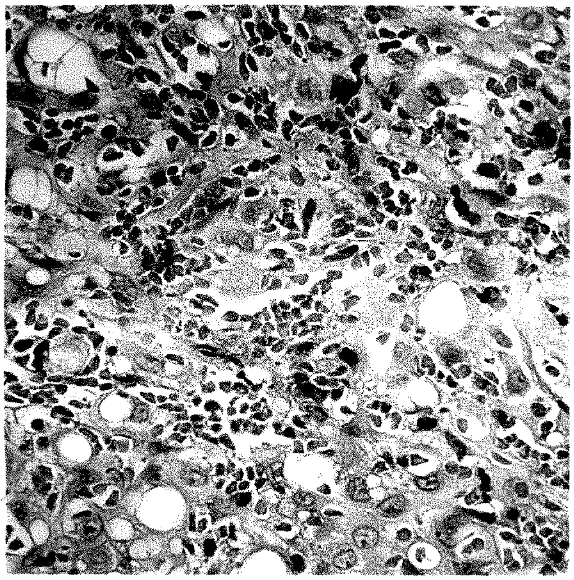

Fig. Angiosarcoma containing numerous vascular spaces lined by atypical endothelium. (H and E × 250).

These tumours appear to present as either a well circumscribed mass or as a tumour diffusely invading tissues of the perineum locally, with or without distant metastases. The outcome of penile angiosarcoma is uncertain since the follow-up of many reported cases is short-term and poorly documented. However, death may occur from 1 week to 5 years after presentation (mean 13 months) and recurrence-free periods of up to 16 years have been reported. Treatment in most cases has been local excision of the tumour combined with lymph node dissection, local radiotherapy and systemic chemotherapy in later cases with more widespread tumour. Complete surgical removal, even of extensive local tumour, seems to offer the best chance of cure and there appears to be no difference in prognosis between patients presenting with diffuse penile swelling and those with a circumscribed nodule.

Thus penile angiosarcoma, albeit an extremely rare lesion, should be considered in the differential diagnosis of patients presenting with penile swelling or nodules.

Acknowledgements

We thank Dr J. L. Dyson, Consultant Histopathologist, Whittington Hospital, and Professor E. Wilson-Jones, Department of Dermatological Pathology, St John's Hospital for Diseases of the Skin, for helpful advice on the pathology of this case and Mr R. J. Morgan for allowing us to report one of his patients.

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Reversal of Duodenal Obstruction due to Metastatic Teratoma by Combination Chemotherapy

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High intestinal obstruction due to malignant disease can usually be circumvented only by surgical intervention. We observed its complete reversal by intravenous combination cytotoxic chemotherapy in a patient with duodenal obstruction due to metastatic testicular teratoma.

Case Report

A 25-year-old, educationally subnormal man had a 6-month history of back pain radiating into the left thigh. Clinical examination and radiographs of his spine were normal, but his back pain continued for a further 4 months. On re-presenting to hospital he was found to have left testicular enlargement. Orchiectomy revealed a poorly differentiated malignant teratoma with areas of trophoblastic differentiation, venous invasion and infiltration of the lower end of the spermatic cord. Circulating α feto protein (AFP) was grossly elevated at 10,230 kU/l (normally <10 kU/l) and serum β human chorionic gonadotrophin (HCG) was also elevated at 182 IU/l (normal <20 IU/l). Two weeks after orchiectomy the patient developed subacute intestinal obstruction. Laparotomy revealed a large retroperitoneal metastasis which encased both the left ureter and renal vein. This tumour was partially debulked and histology confirmed metastatic teratoma; 10 days after laparotomy he again developed intestinal obstruction and ultrasonography revealed a large retroperitoneal mass causing left hydronephrosis, and 2 liver metastases. Barium meal showed obstruction at the third part of the duodenum which was encased by extrinsic tumour. He was referred to our institution.

Cisplatin 30 mg and etoposide (VP16) 100 mg intravenously (IV) were given daily for 3 days with bleomycin 15 mg IV on the second day. Two weeks later, VP16 160 mg IV daily for 5 days, actinomycin D 0.5 mg IV on days 3, 4, 5 and cyclophosphamide 800 mg IV on day 5 were given. The clinical features of intestinal obstruction completely reversed. Cytotoxic chemotherapy was then given for a total of 11 weeks with vincristine, methotrexate with folinic acid rescue, and bleomycin all by IV injection or infusion, alternating weekly with VP16 and cisplatin with IV hydration. Circulating AFP and β HCG both fell to normal by the sixth week of weekly chemotherapy and remained normal thereafter. After completion of chemotherapy, CT scans were normal apart from a left retroperitoneal mass of approximately 2 cm maximum diameter, which was presumed to be inactive tumour. Normally we would recommend surgical removal but the patient had severe anxiety about further surgery, so irradiation to the residual mass was given, since radiotherapy is known to be effective in sterilising minimal tumour following chemotherapy (Read *et al.*, 1986). The patient remains well with no clinical, biochemical or radiographic evidence of disease reactivation 14 months after completion of all therapy and is likely to be a long-term survivor.

Comment

We have shown that intestinal obstruction due to chemosensitive metastatic teratoma can be rapidly and completely reversed by combination cytotoxic chemotherapy. This case illustrates the difficulty and delay in establishing a diagnosis of metastatic testicular malignancy (Oliver, 1985). Back pain as a major presenting symptom led to significant delay in the diagnosis of metastatic testicular malignancy (Cantwell *et al.*, 1987). This case also supports the findings in a randomised trial (Javadpour *et al.*, 1982) that the value of debulking surgery before chemotherapy in metastatic teratoma is unproven. Debulking surgery before chemotherapy for metastatic disease may delay the initiation of effective chemotherapy and may accelerate progression of disease (Lange *et al.*, 1980).

Patients with metastatic testicular malignancy should receive combination chemotherapy as soon as possible after orchiectomy.

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Requests for reprints to: B. M. J. Cantwell, University Department of Clinical Oncology, Newcastle General Hospital, Westgate Road, Newcastle upon Tyne NE4 6BE.

British Journal of Urology (1989), **63**, 443
0007-1331/89/0063-0443/$10.00

Point of Technique

Suprapubic Catheterisation

W. T. LAWRENCE, P. H. McQUILKIN and D. MANN,
Department of Urology, City Hospital, Nottingham

Many types of suprapubic catheter in use today require fixing at skin level (often with stitches) to prevent them from being pulled out. We have developed a new trocar and sheath to insert a Foley type catheter into the bladder via the suprapubic route. The balloon of the catheter retains it in position and extra fixation is not needed.

The Nottingham suprapubic catheter introducer has 2 parts: a central trocar with a sharp tip and comfortable handle, and an outer sheath with pull-tab and tear-off strip (Fig. 1). The device is disposable and there are 2 sizes, one for 12 and the other for 16F catheters.

Technique

After infiltrating the skin with anaesthetic, the position of the bladder is confirmed by inserting a 21 gauge needle. If urine is not obtained by this exploratory tap it is unwise to proceed.

There are 4 simple steps for catheterisation. (1) A 1-cm transverse skin incision is made. (2) The assembled introducer (trocar and sheath) is inserted into the bladder along the previous needle track. This manoeuvre is facilitated by rotating the introducer during advancement. (3) The trocar is removed, placing a finger over the end of the sheath to prevent urinary leakage. A Foley catheter is passed through the sheath into the bladder and its balloon is inflated with 5 to 10 ml of fluid. (4) Having withdrawn the sheath, the strip is torn down to remove it from the catheter (Fig. 2).

If there is excessive scar tissue the small skin incision may be deepened through the rectus sheath before inserting the trocar.

This simple technique avoids the use of stitches and dressings and is readily accepted by patients, nurses and doctors.

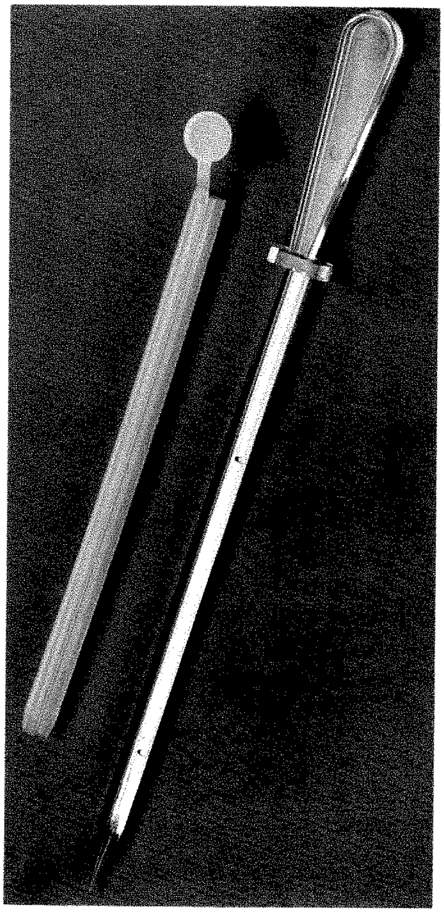

Fig. 1 The Nottingham suprapubic catheter introducer. Trocar (right); sheath (left).

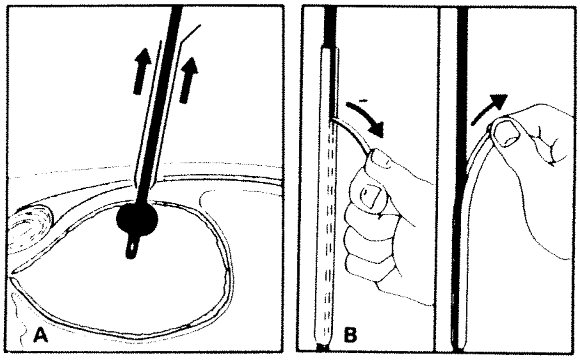

Fig. 2 (A) Balloon inflated. (B) Sheath withdrawn and then removed.

Based on a Poster Demonstration at the 44th Annual Meeting of the British Association of Urological Surgeons in Buxton, June 1988

Requests for reprints to: P. H. McQuilkin, Femcare Ltd, Bar Lane Industrial Park, Bar Lane, Basford, Nottingham NG6 0JA.

British Journal of Urology (1989), **63**, 444–446
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0007-1331/89/0063-0444/$10.00

Correspondence

re Oxybutynin: is it safe? R. J. Baigrie, J. P. Kelleher, D. P. Fawcett and A. W. Pengelly. *Br. J. Urol.*, **62**, 319–322, 1988.

Letter to the Editor. Named-patient supply of unregistered drugs is a correct and proper form of prescription. The medico-legal implications of such practice are quite clear and the prescribing doctor should have no fear of repercussions provided he can respond affirmatively to the following two questions:

(1) Is this the only treatment left to me? In other words, have I exhausted all other approved drugs?
(2) Do I know all there is to know about the unapproved drug? Have I had a satisfactory statement from the drug company on the benefits and known risks?

It is true that the primary responsibility in prescribing unlicensed drugs lies with the prescribing physician. The only clearly defined responsibility a drug company has is to product liability, *i.e.* free from manufacturing defects. However, a drug company does have an ethical responsibility in ensuring its research products are used appropriately. It is my practice to approve named-patient use of my company's unlicensed products only after personal discussion with the responsible doctor. I need to assure myself the drug is being appropriately prescribed. Too often doctors want to prescribe a new research drug because it is the latest "toy". I would not like defending such practice in court. It would amount to negligence in my mind, if something were to go wrong. Regarding Oxybutynin itself, the widespread named-patient use of the drug is legend. If I were a doctor thinking of prescribing it, I would carefully question the companies concerned why, after all these years, it has not got a licence, rather than encourage them to apply for one.

Dr Richard Wild,
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Reply by Mr A. W. Pengelly. I wish to make two comments in reply to Dr Richard Wild's letter. Firstly, we performed our retrospective review because of the difficulty in answering Dr Wild's second question, *i.e.* do we know all there is to know about the unapproved drug? Secondly, the warnings in Dr Wild's final paragraph should of course be well heeded, but it should not be forgotten that his company market Terodiline, which is one of the principal competitors to Oxybutynin.

re One-stage pedicle scrotal flap urethroplasty. H. A. De Carvalho and R. L. Ferreira. *Br. J. Urol.*, **62**, 279–280, 1988.

Letter to the Editor. The above "Point of Technique" article reminds me that I first described this procedure in 1967. The second patient described in the original paper underwent resection of the bladder neck and prostate in 1972 without difficulty and the urethral calibre was quite adequate. An ascending urethrogram in 1981 showed that there had been considerable reduction in the excess skin originally inserted. When seen in September 1988 the patient's stream was as good as ever and I was able to pass a 12/15 E bougie without difficulty.

Technically I stressed that a scrotal flap should always be tapered at each end to form a V so that there is no sudden edge at the point of anastomosis proximally or distally that may present an obstructive flap or stricture. Scrotal skin minimises hair growth and depilation has not been necessary. The operation is useful throughout the length of the bulbous and penile urethra for recurrent or resistant strictures not cured by internal urethrotomy. The use of the pedicle flap converted to a tube in the urethra was also described in the first case of my original article.

Reference

Yaxley, R. P. (1967). One stage urethroplasty. *Aust. N. Z. J. Surg.*, **36**, 332–336.

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Australia.

Reply by H. A. De Carvalho. I regret that my article contained the inaccurate reference to Mr Orandi as the first to describe this procedure. It is probable that many more urologists are under the same impression. Now that the real father of the technique is known, I shall make sure in future that the correct reference is quoted.

re Non-operative diagnosis of renal sinus lipomatosis simulating tumour of the renal pelvis. Y. T. Chan, F. L. Chan, K. K. Ho and W. D. Ng. *Br. J. Urol.*, **61**, 265–266, 1988.

Letter to the Editor. In this Case Report the authors concluded that the suspicious filling defects seen in the intravenous urogram were due to renal sinus lipomatosis. Although renal sinus has been diagnosed by CT scan, its relevance to the filling defects of intravenous urography remains doubtful. In fact, the appearance of the IVU is highly suggestive of an inadequately filled large pelvis. This radiological finding is known as "flabby pelvis" (Witten *et al.*, 1977). It can be confirmed by achieving adequate filling of the renal pelvis by retrograde pyelography. This leads to the complete disappearance of the radiolucent shadows of a flabby pelvis. Incidentally, in the case reported the filling defects vanished during retrograde pyelography. It supports our belief that renal sinus lipomatosis may not have been the real cause of the filling defects seen in the IVU.

Reference

Witten, D M., Myers, G. H. and Utz, D C (eds) (1977) The normal urogram In *Emmett's Clinical Urography* Fourth edition. Volume I. Chapter 8, pp 481–564 Philadelphia· Saunders

P. K. Arora,
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Reply by Y. T. Chan et al. Admittedly, a filling defect on an intravenous urogram, which disappears when the pelvicaliceal system is forcefully distended during retrograde pyelography, may be attributable to under-filling in a flabby pelvis. However, a similar event may occur in the presence of external compression and this has been clearly demonstrated to be the case in our patient by the accompanying computed tomogram—the section shows a smooth fat density mass bulging into the pelvis. It is conceivable that low pressure compression, occasioned by the presence of over-abundant renal sinus fat, readily yields to the pressure of retrograde injection of contrast. Radiographic filling defects in an incompletely filled flabby pelvis are characteristically irregular, haphazardly arranged and have a blurred margin, most of which is contiguous with the contour of the opacified pelvis. These features were distinctly lacking in our case.

re Bilateral testicular germ cell tumours: an increasing incidence and prevention by chemotherapy. Joyce Thompson *et al. Br. J. Urol.*, **62**, 374–376, 1988.

Letter to the Editor. The authors of the above article confirm the impression of many investigators that the incidence of bilateral testicular germ cell tumours is increasing. However, their conclusion that bilateral testicular tumours (BTT) can be prevented by chemotherapy needs further consideration. There are at least 2 pieces of evidence proving their conclusion incorrect.

Firstly, there are several clinical reports with observations of BTT arising after chemotherapy (Dieckmann, 1988). In our own series as many as 5 of 10 sequential BTT developed after chemotherapy. Secondly, carcinoma *in situ* of the testis, which has been recognised as the uniform precursor lesion of all germ cell tumours (Skakkebaek *et al.*, 1987) and which can be detected in 5.4% of all contralateral testes (Van der Maase *et al.*, 1986), is not completely eradicated by chemotherapy. Von der Masse *et al* (1988) recently reported the recurrence of carcinoma *in situ* in a control biopsy 24 months after cessation of chemotherapy. This case has to be regarded as the morphological and theoretical clue to the clinical observation of BTT despite chemotherapy. Most obviously, carcinoma *in situ* is only suppressed temporarily by chemotherapy and thus the occurrence of BTT is probably only delayed but not prevented by cytotoxic drugs. From many clinical reports it is known that BTT may arise even after very long intervals. We encountered one patient who developed his second tumour 20 years and 7 months after the first. At least 10 additional cases with long intervals have been reported (Dieckmann *et al.*, 1988).

Thompson *et al.* have based their conclusions on an observation period of only 8 years, which is too short for a reliable estimate of the frequency of BTT. As a result, conclusions drawn from these data with immediate relevance to patient care, *e.g.* follow-up examination of the contralateral testis, might be premature and should therefore be considered with caution.

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Reply by G. M. Mead. We are grateful for this useful comment on our data. The additional information to which Dr Dieckmann refers, most of which has been published since our data were submitted for publication, is very pertinent.

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re The value of cystourethroscopy in the investigation of microscopic haematuria in adult males over 40 years. A prospective study of 100 patients. D. J. Jones *et al. Br. J. Urol.*, **62**, 541–545, 1988.

Letter to the Editor. I read with interest the above article. While I accept that cystourethroscopy may be of minimal diagnostic value in young men with microscopic haematuria, the following case illustrates the fact that unexpected findings do occur.

Eighteen months ago a young man of 28 was referred to me by his firm's medical adviser. He was a merchant banker who was about to take up a post in Europe and on routine medical examination was discovered to have microscopic haematuria. Further medical advice was suggested. He consulted his General Practitioner, who felt that nothing further should be done, but the medical adviser subsequently referred him to me.

He was an extremely fit young man with no positive physical signs, a normal intravenous urogram and microscopic haematuria in a number of urine specimens. In view of these findings I advised cystourethroscopy. To my considerable surprise this was grossly abnormal. The bladder was oedematous and erythematous, with granulomatous lesions scattered all over the bladder, and with no further history I wondered if he could have tuberculosis. Multiple biopsies showed gross active lesions of schistosomiasis with live ova present.

Further discussion with the patient revealed that he had, 2 years earlier, gone off with a team from his bank to the North Yemen. They had had one day off and had gone up country, where he paddled in a local lake on one occasion only. He was treated by a single dose of Praziquantel and at review cystoscopy his bladder had healed completely. He has remained well at follow-up.

Certainly at his initial consultation he had seen no reason to mention this visit and he had no symptoms whatsoever, but maybe this one instance does underline that there can be serious causes of asymptomatic microscopic haematuria and that there can be considerable value in the investigation of these patients.

In the past I have also seen patients presenting in this age group with transitional cell tumours, malakoplakia and stricture who have in fact been asymptomatic.

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British Journal of Urology (1989), 63, 447–448

Notices

British Association of Urological Surgeons

President: R. T. Turner-Warwick, DSc, DM, MCh, FRCP, FRCS, FACS

Annual Meeting: St Helier, Jersey, Channel Islands. 20–23 June 1989

All correspondence to: Hugh N. Whitfield, MChir, FRCS, Honorary Secretary, British Association of Urological Surgeons, Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN.

C.-E. Alken Prize

An endowment fund has been established to further clinical work and research in the field of Urology by presenting an annual award of SwF 10,000 for outstanding scientific endeavours. The award will be for an unpublished work in the field of Urology. An award certificate will also be presented. The prize money may be divided among several contributors.

The papers may be written in either German or English and three copies must be submitted by 30 September 1989 to: Stiftungsrat C.-E. Alken-Stiftung, Advokaturbüro Dr F. Kellerhals, Bundesplatz 4, CH-3011 Bern, Switzerland.

Each submission must be affixed with a code word and must not bear the author's name. In addition, a sealed envelope labelled with the code word is to be included, containing on a separate sheet of paper the author's name and professional standing, together with the code word.

The adjudicators for the award will be the Board of Directors of the endowment fund and their decision will be final.

Shackman Travelling Fellowship 1990

Applications are invited from Medical Practitioners registered in the United Kingdom who are Senior Registrars in an accredited training programme in urology or Consultant Urological Surgeons of no more than 5 years' duration. Applicants of equivalent university status will also be considered.

The Fellowships are intended to provide sufficient support to enable the holder to undertake a period of study, either in the United Kingdom or abroad, for a period of not less than 6 weeks.

The subject to be studied must be related either to urology or to renal transplantation and may be either a laboratory or a clinical investigation.

The closing date for applications is 1 September 1989.

Further particulars from and all correspondence to: Taylors, Solicitors, 119 High Street, Newmarket CB8 9AG.

Silver Jubilee British Congress of Obstetrics and Gynaecology

Queen Elizabeth II Conference Centre, London. 4–7 July 1989

Further information from: Caroline Roney, Congress Organiser, Congress House, 65 West Drive, Sutton, Surrey SM2 7NB.

Edinburgh Urological Festival

A Joint Postgraduate Urological Meeting: Edinburgh University Department of Surgery (WGH) and Department of Urology, University of California, Davis

Edinburgh. 23–26 August 1989

The programme will consist of review lectures by invited speakers from the USA and Europe, with short papers by participants on the following topics: Superficial Bladder Cancer; Bladder Dysfunction; Reconstructive Surgery; Infertility and Sexual Dysfunction; Neo-adjuvant Chemotherapy; Flow Cytometry in Urology.

Further particulars from: Urological Festival Secretary, University Department of Surgery (WGH), Western General Hospital, Crewe Road, Edinburgh EH4 2XU, UK *or* Professor A. Stone, Department of Urology, University of California, Davis, Sacramento, USA.

Athenian Days of Urology

Athens, Greece. 6 and 7 May 1989

Further information from: Professor C. Dimopoulos, Laikon Hospital, 11527 Athens, Greece.

54th Congress of the Belgian Society of Urology

Brussels, Belgium. 27–28 May 1989

The topic will be "Lower Urinary and Genital Pathology in Children."

Further particulars from: Dr F. F. Wart, C.H.U.-I.M.C.A.G., Division of Urology, Boulevard Zoe Drion 1, B-6000 Charleroi, Belgium.

Congress of the Spanish Association of Urology

Toledo, Spain. 28–31 May 1989

Further information from: REYCOSA, Parque de la Colina, 6, bajo dcha, 28043 Madrid, Spain.

XXVIth Congress of the European Dialysis and Transplant Association—European Renal Association

Göteborg, Sweden. 11–15 June 1989

Further information from: General and Scientific Secretariat, Transplant Unit, Department of Surgery, Sahlgrenska Hospital, S-413 45 Göteborg, Sweden.

S.U.W.O. (Urological Research Foundation) Symposium on Paediatric Urology

Rotterdam, The Netherlands, 30 June and 1 July 1989

The following topics will be discussed: ureteric obstruction, duplication of kidney and ureter, neurogenic bladder dysfunction, anorectal malformation and vesicoureteric reflux.

Further information from: Mrs S. Wolff, Department of Urology, University Hospital Dijkzigt, Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands.

Annual Meeting of the Swiss Society of Urology

Aarau, Switzerland. 21–23 September 1989

The main themes will be Renal Carcinoma and Ultrasound in Urology.

Further information from: Professor R. Tscholl, Urologische Klinik, Kantonsspital, CH-5001 Aarau, Switzerland, or Professor D. Hauri, Urologische Klinik, Universitätsspital, CH-8091 Zürich, Switzerland.

Fourth Steglitz Pediatric Surgical Symposium: Laser Application in Children

Berlin, West Germany. 10 and 11 November 1989

Further information from: Dr Felix Schier, Department of Pediatric Surgery, Free University of Berlin, Hindenburgdamm 30, 1000 Berlin 45, West Germany.

Archivos Españoles de Urologia

Readers are advised that the above journal now has a new publisher. To ensure that subscribers continue to receive their copies of the journal they are requested to contact Ediciones BOK, S.A., Pilar Millan Astray, 4, esc. 2, 1.°A, 28009 Madrid, Spain.

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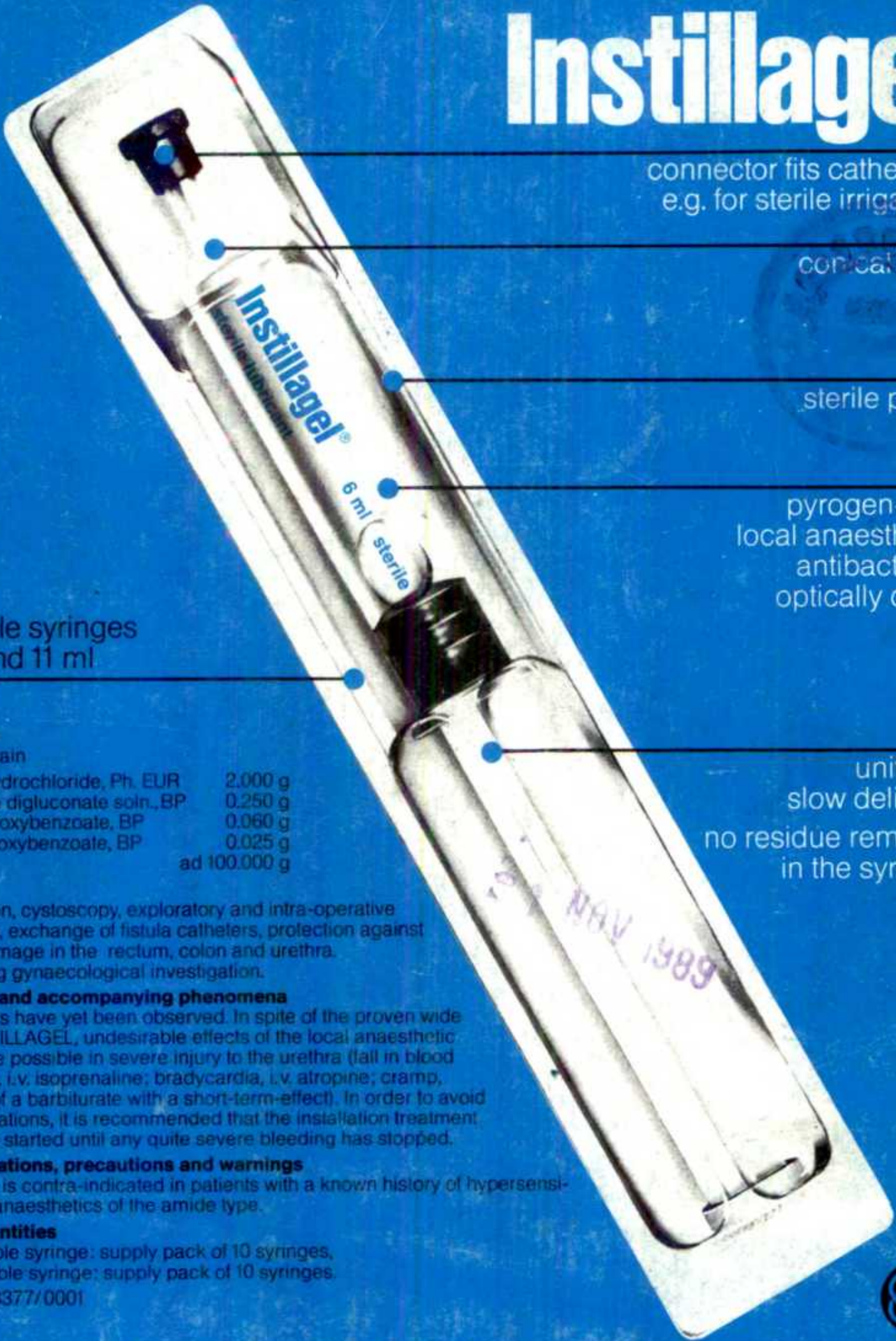

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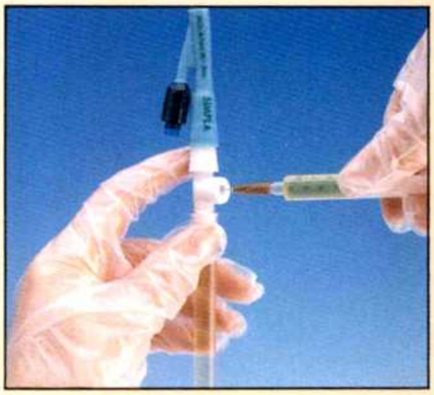

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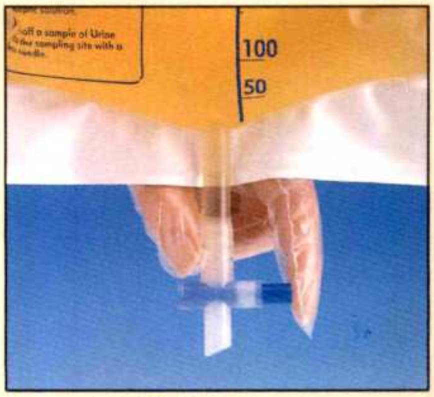

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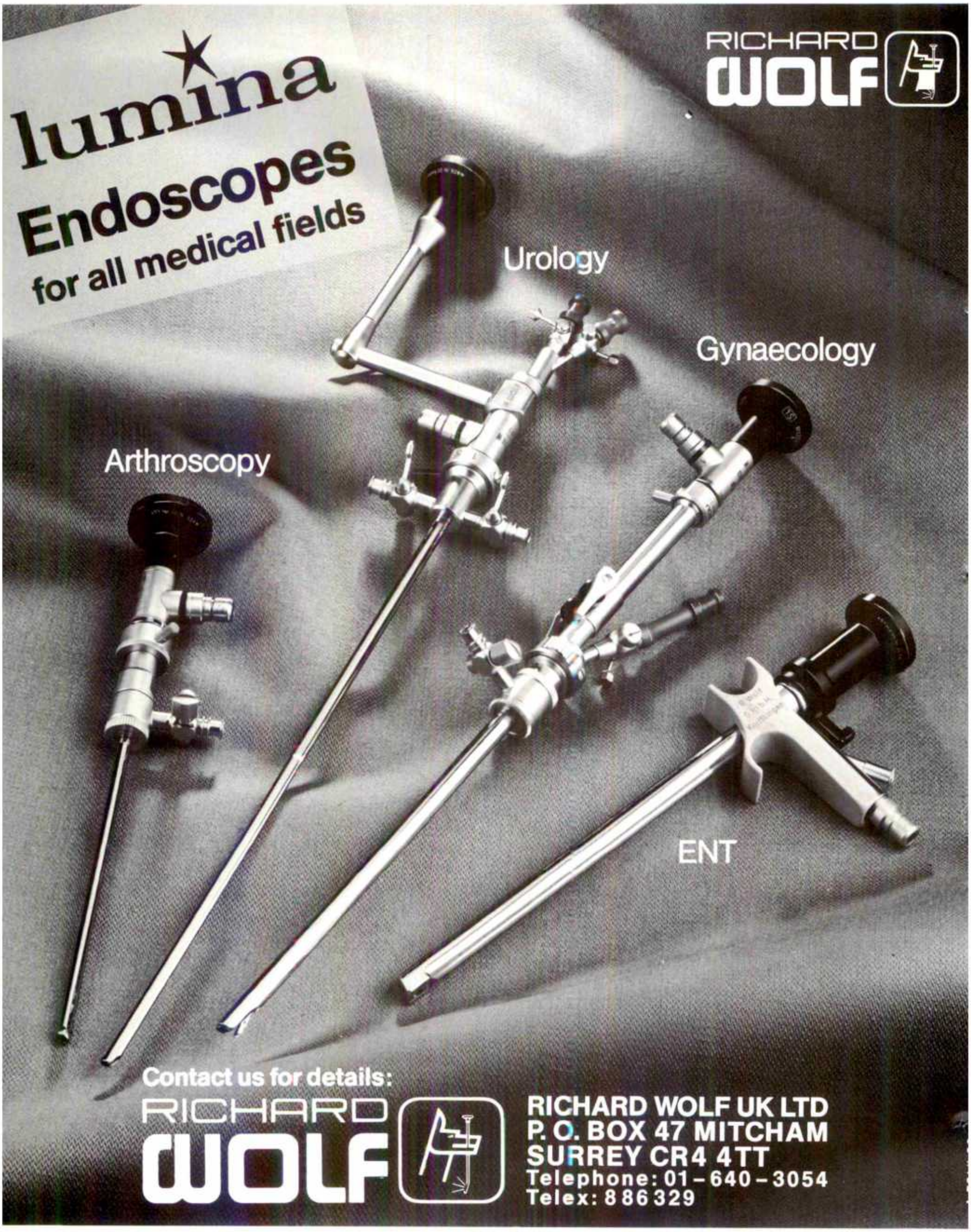

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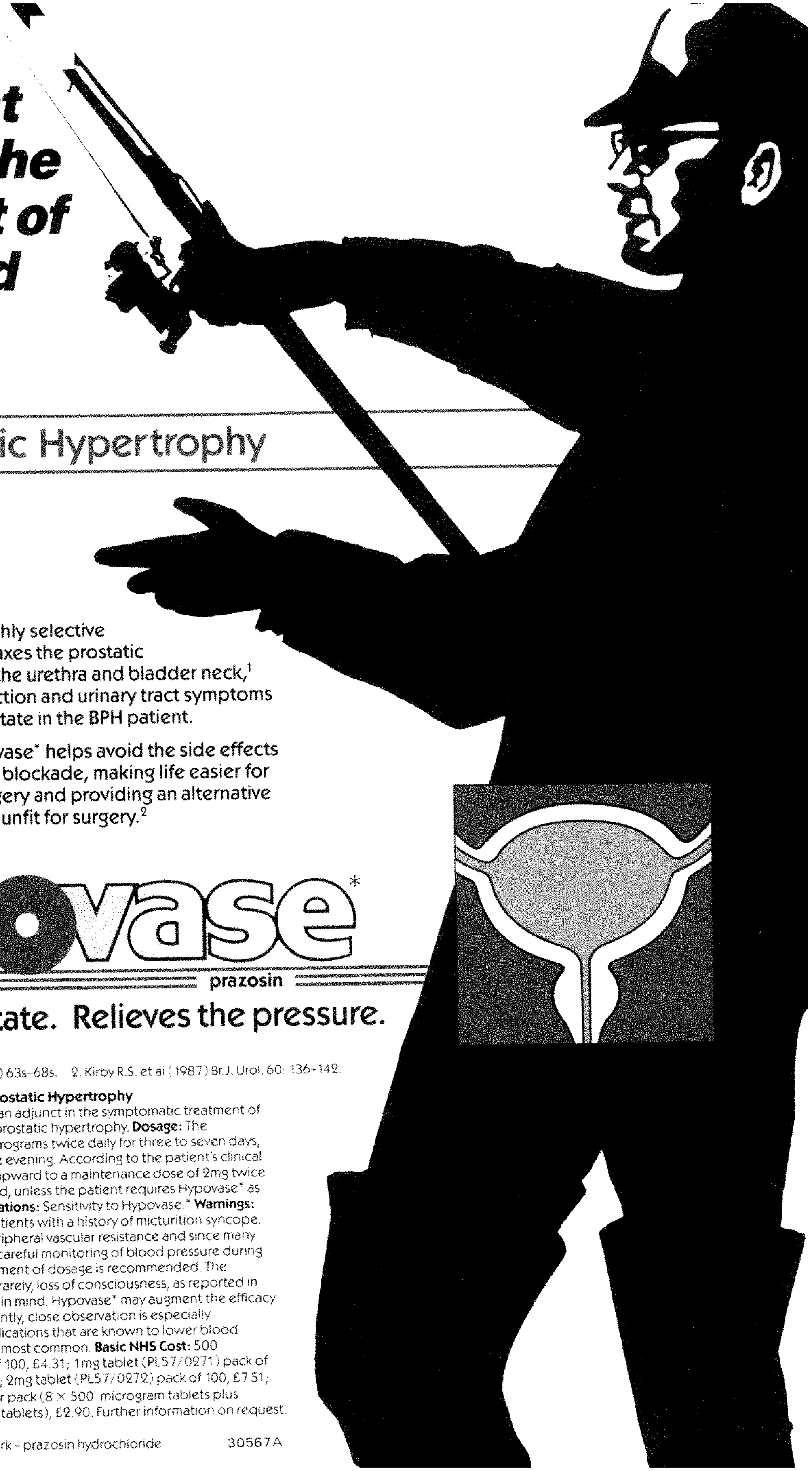

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1. Caine M. (1986) Clin. Sci. 70 (Suppl. 14) 63s–68s. 2. Kirby R.S. et al (1987) Br.J. Urol. 60: 136–142.

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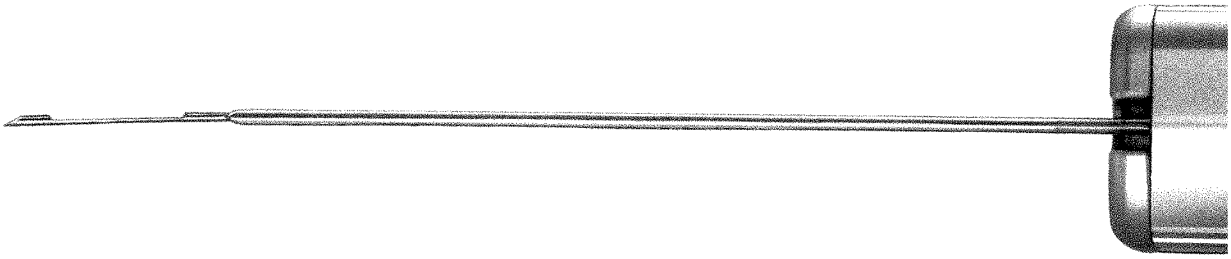

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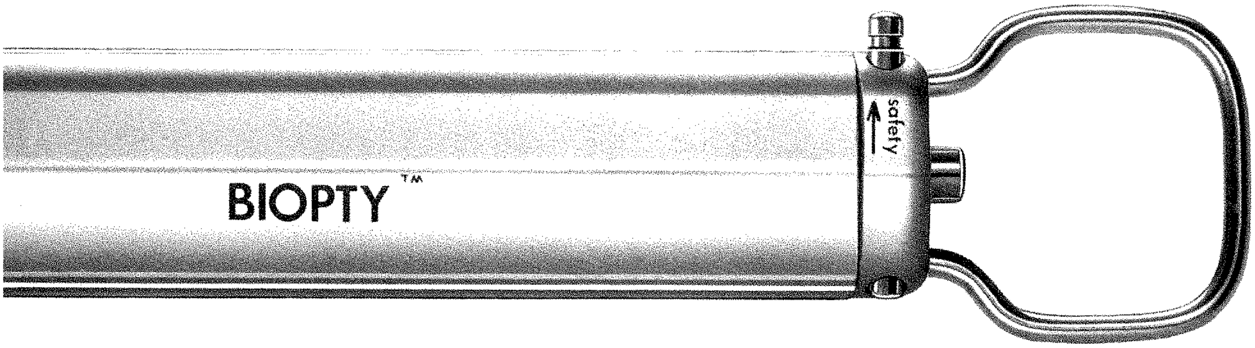

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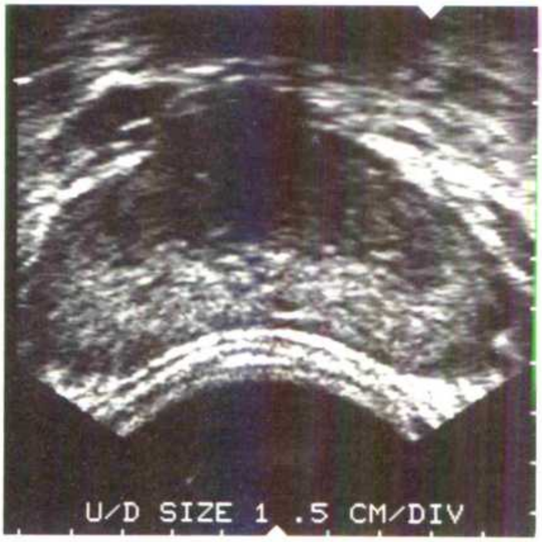

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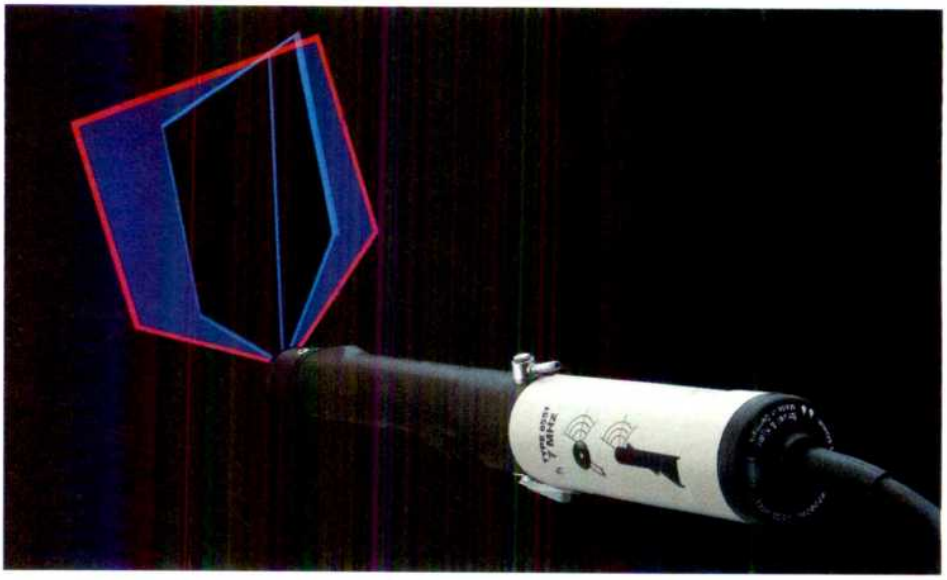

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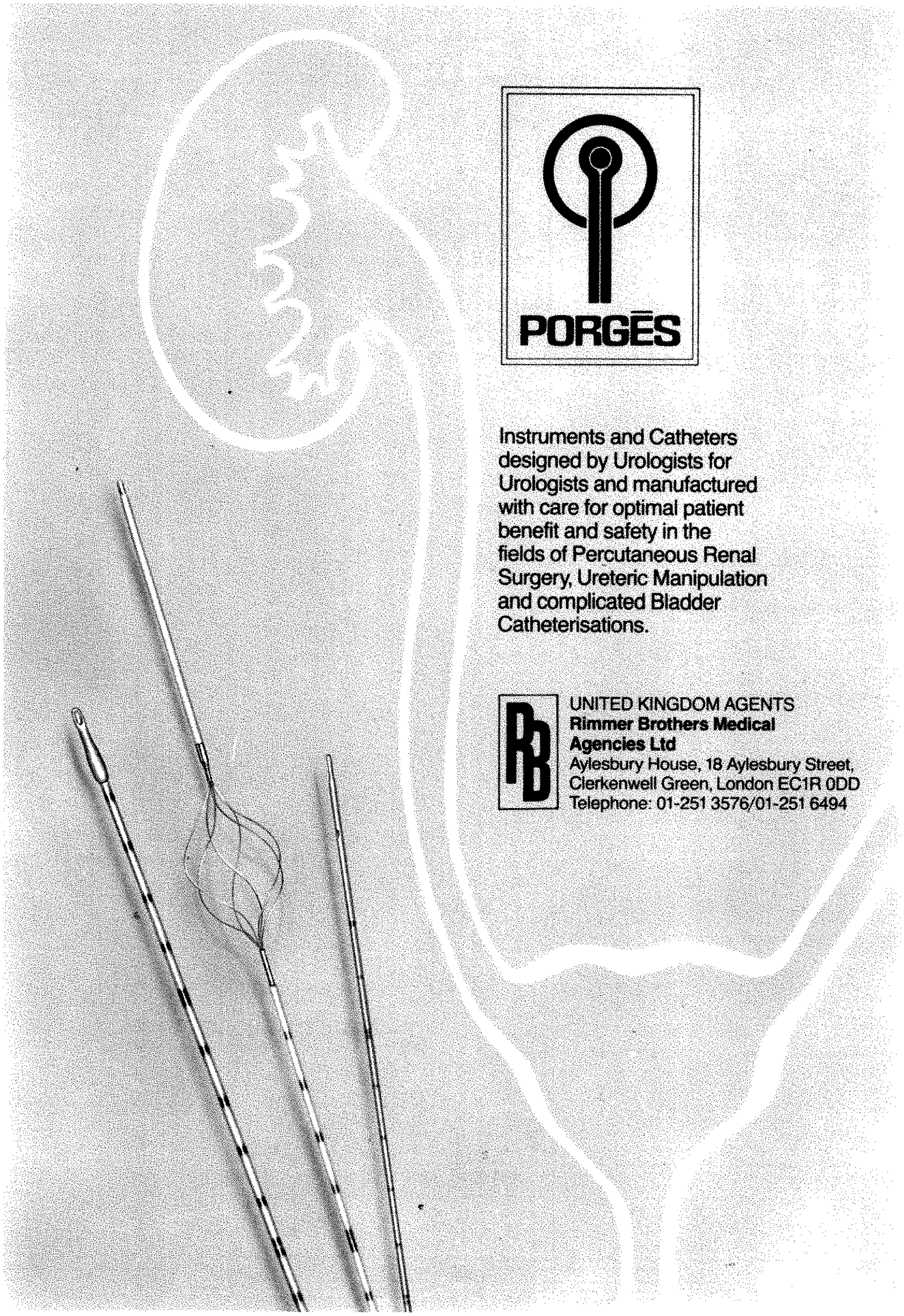

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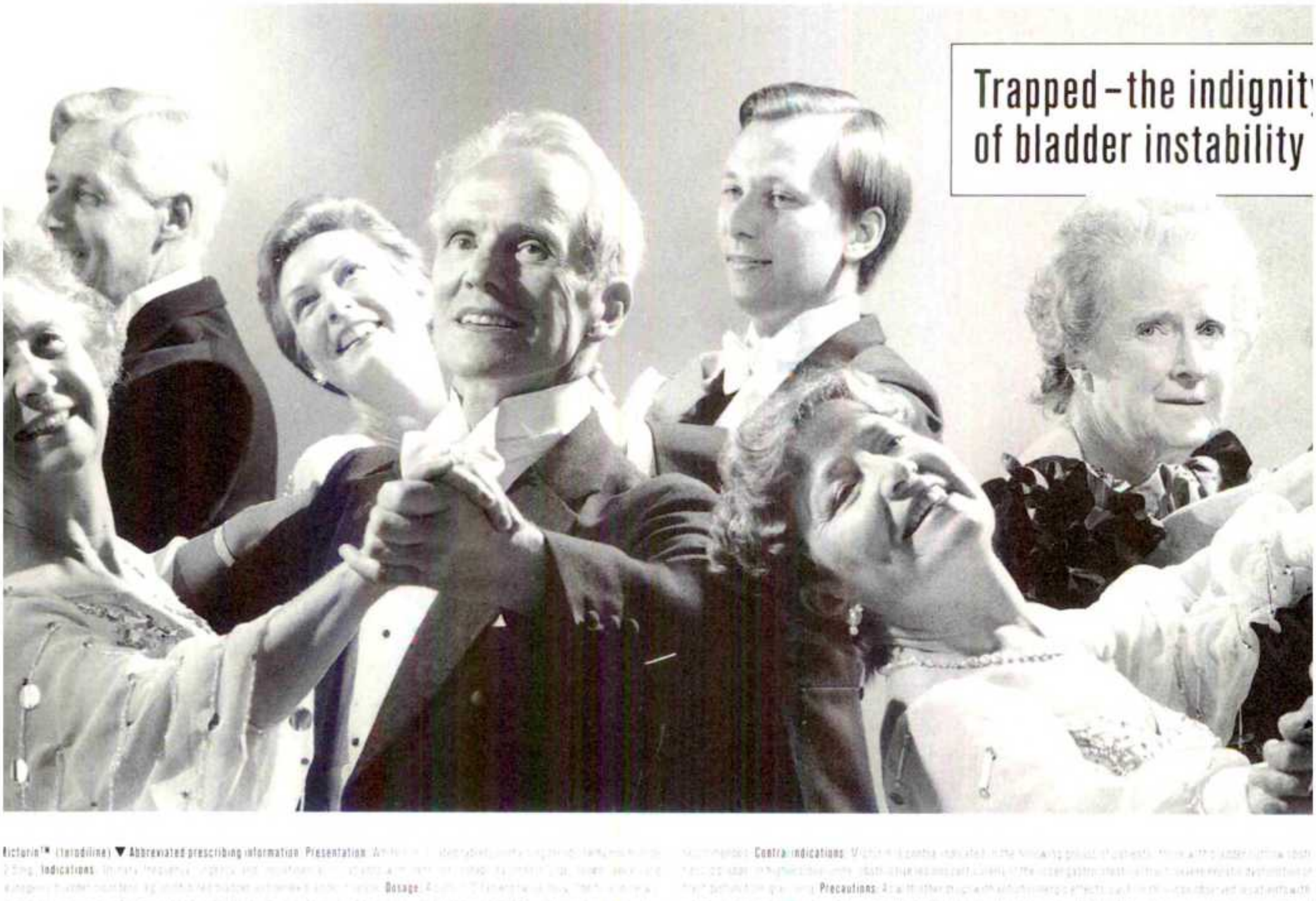

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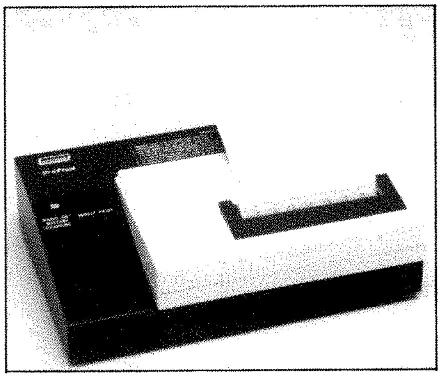

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Are Prophylactic Antibiotics Necessary during Extracorporeal Shockwave Lithotripsy?

B. PETTERSSON and H.-G. TISELIUS

Department of Urology, University Hospital, Linköping, Sweden

Summary—A randomised clinical study was carried out on patients admitted for ESWL treatment in order to establish the requirement for prophylactic treatment with antibiotics during this procedure. Patients with clinical signs of urinary tract infection, evidence of infectious stones or a positive urine culture were excluded. All other patients were consecutively randomised into 3 groups which were given either trimethoprim + sulphamethoxazole or mecillinam (Group A), methenamine hippurate (Group B), or no treatment at all (Group C). Evaluation with respect to clinical signs of infection was done immediately after the treatment and 4 weeks later. In addition, a urine culture was performed 2 weeks after ESWL, *i.e.* 1 week after completing treatment with antibiotics and methenamine hippurate.

With respect to infectious complications there were no differences between Groups A and C, between Groups B and C or between Group A and B + C, whereas an unexplained slightly higher infectious rate was recorded for Group B compared with Group A. In all patients the occurrence of bacteriuria was low (6.7%) despite the fact that almost 30% of patients had a ureteric catheter during the ESWL procedure. Patients with ureteric catheters did not present with more infectious complications than those without. All patients had a bladder catheter during ESWL. It was concluded that prophylactic treatment with antibiotics during ESWL treatment is unnecessary in all situations where an infectious aetiology is unlikely.

In order to avoid infectious complications in patients treated with ESWL for renal stones, prophylactic antibiotics are frequently administered (Schmiedt and Chaussy, 1984; Eisenberger *et al.*, 1987; Libby *et al.*, 1988). The reasons for this are firstly to counteract bacterial contamination of the urinary tract from the bladder and/or ureteric catheter (Lingeman *et al.*, 1986; Schaeffer, 1986) and secondly to eliminate septic complications from bacteria that might be released from the disintegrated stone (Riehle *et al.*, 1986; Lingeman, 1987). Septic complications do occur and have been described occasionally after ESWL (Riehle *et al.*, 1986; Eisenberger *et al.*, 1987; Fuchs and Chaussy, 1987; Politis and Griffith, 1987). However, the majority of stones in these patients are of non-infectious origin and do not contain bacteria. After 2 years of routine antibiotic treatment of all patients with non-infectious stones, without recording any significant infectious complications, we decided to investigate the clinical value of this regimen. The present report summarises our experience from a randomised trial with or without prophylactic measures in association with ESWL treatment.

Patients and Methods

During a period of 3 months, 149 patients at our ESWL unit were randomised into 3 different groups. Group A comprised 57 patients (44 men and 13 women). This group was treated mainly according to our routine programme with a combination of trimethoprim 0.16 g and sulphamethoxazole 0.8 g (Bactrim) twice daily. Patients who were allergic to sulphonamide derivates were given mecillinam 0.2 g (Selexidin) 3 times daily. Group B comprised 47 patients (31 men and 16 women). These patients were given methenamine hippurate 1 g (Hiprex) 3

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times daily, whereas Group C, comprising 45 patients (37 men and 8 women), underwent ESWL without any prophylactic measures. All substances were administered orally, starting on the evening before treatment and continued during the next 7 days.

During the same period, 23 patients were excluded from randomisation because of suspected or evident infection; 12 of these patients had staghorn stones, 4 a positive dip-test, 4 a recent history of urinary tract infection and 3 a percutaneous nephrostomy catheter.

All patients were given fluid infusion and 20 mg of frusemide intravenously during the ESWL procedure. In addition, 20 mg of frusemide were given intravenously on the same evening. For the next 3 to 4 days frusemide was administered orally in a dose of 40 mg daily.

All procedures were performed with a Dornier lithotripter type HM3, equipped with the original reflector and generator system. The voltage varied between 18 and 23 kV, with the majority of patients treated at 18 kV. The number of shockwaves ranged between 800 and 2025. Most patients were treated under epidural anaesthesia and only occasionally under general anaesthesia.

A bladder catheter was inserted in all patients just before ESWL and it was removed the same afternoon. When a ureteric catheter was required this was introduced in the morning of the day that ESWL was performed.

A urine culture was performed on the day before and 2 weeks after ESWL. The patients were observed carefully for any signs of infection (fever, septicaemia, urinary tract infection). Their history during the next 4 weeks was summarised at an out-patient visit.

The result of treatment was judged by a plain radiograph (KUB) on the day after treatment and by intravenous urography 4 weeks later.

The distribution of the patients' age, stone size and position of stones in the renal tract was similar in all groups (Table 1) (Fig.).

Table 1 Details of Patients and Stones

	Group A	*Group B*	*Group C*
No. of patients	57	47	45
Mean age ± SD	49 ± 12	48 ± 12	48 ± 12
Largest stone diameter (mm) Mean ± SD	15 ± 8	16 ± 7	15 ± 8
Renal pelvis	20 (35%)	17 (36%)	11 (24%)
Upper calix	4 (7%)	2 (4%)	8 (18%)
Middle calix	5 (9%)	5 (11%)	5 (11%)
Lower calix	18 (32%)	17 (36%)	19 (42%)
Ureter	10 (17%)	6 (13%)	2 (5%)

The 3 groups were further divided according to their ESWL type (Tiselius *et al.*, 1988), where type A comprises kidneys with 1 stone less than 6 mm in diameter. Type B has 1 stone with a diameter between 6 and 20 mm or 2 to 3 stones, the largest with a diameter not exceeding 10 mm. Type C has 1 stone with a diameter of 21 to 30 mm, 2 to 3 stones with a maximum diameter of 20 mm, or more than 3 stones with a maximum diameter of 10 mm. Type D has 1 stone with a diameter of more than 30 mm (excluding staghorn stones), 2 to 3 stones with a largest diameter above 20 mm, or more than 3 stones where at least 1 has a diameter of more than 10 mm. Type F has 1 or several ureteric stones. Most patients belonged to types B (64%) C (18%) and F (12%) (Table 2).

Positive urine cultures before treatment were recorded in 1 patient from Group A, 2 from Group B and none from Group C.

In 44 patients (30%) a ureteric catheter was inserted before treatment.

The inclusion of patients in Groups A, B, and C was determined by the last figure in the patient's birthday according to the corresponding figure in a table of random numbers. The chi-squared test was used for statistical analysis.

Results

In all groups the follow-up rate with urine culture

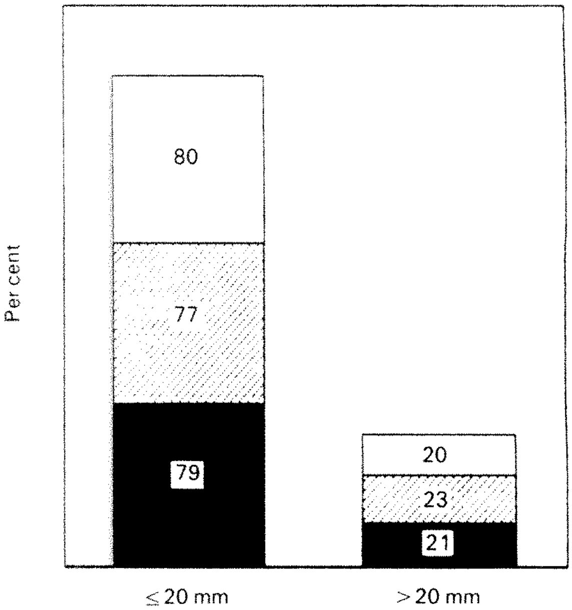

Fig. Distribution of stones with maximum diameter below and above 20 mm in patients from Group A ■, Group B ▨ and Group C ☐.

Table 2 ESWL Types

	ESWL type				
Group	*A*	*B*	*C*	*D*	*E*
A	1	34	11	1	10
B	0	30	9	2	6
C	2	32	7	2	2
Total	3	96	27	5	18

after 2 weeks and clinical evaluation after 4 weeks was very good, varying between 94 and 100%. Although 3 patients had positive pre-treatment urine cultures (1 in Group A and 2 in Group B), only 1 of them (a patient from Group B) had a positive culture at follow-up 2 weeks after ESWL.

As shown in Table 3, 10 patients had bacterial growth in their urine after treatment.

In terms of positive urine culture or clinical signs of infection there was no significant difference between Groups A and C or between Groups B and C. However, the infectious rate was significantly higher in Group B than in Group A ($P<0.05$). When Group A was compared with Groups B+C the result did not differ significantly.

A ureteric catheter was commonly used to facilitate the treatment of stones in the ureter as well as small stones in the kidney; 44 patients had a catheter passed before treatment, 15 in Group A, 17 in Group B and 12 in Group C. As shown in Table 4, the frequency of infectious complications was not higher in patients with ureteric catheters. In contrast, there were more patients with bacteriuria and clinical infection in the catheter-free group. In the whole series a positive urine culture after 2 weeks was obtained in 2 patients with and 8 without a ureteric catheter. After 4 weeks, clinical signs of infection were recorded in 1 and 5 patients respectively.

The result of ESWL treatment was comparable among patients from the 3 groups (Table 5) as judged from radiographic control in 141 patients (95%) 4 weeks after ESWL.

Table 3 Bacteriuria and Clinical Signs of Infection

	Group A	*Group B*	*Group C*
Positive urine culture before treatment	1	2	0
Positive urine culture 2 weeks after treatment	2	6	2
Clinical infection during hospital stay	0	1	0
Clinical infection at 4 weeks' follow-up	1	4	1

Table 4 Infectious Complications in Patients with (UC) or without (0) Ureteric Catheter

	Group A		*Group B*		*Group C*	
	UC	*0*	*UC*	*0*	*UC*	*0*
Clinical infection during hospital stay	0	0	1	0	0	0
Positive urine culture 2 weeks after treatment	0	2	1	5	1	1
Clinical infection at 4 weeks' follow-up	0	1	0	4	1	0

Table 5 Result of Treatment 4 Weeks after ESWL (%)

	Group A	*Group B*	*Group C*	*Total*
Stone-free	70	52	56	60
Fragments ≤ 3 mm	11	14	21	15
Fragments > 3 mm	19	34	23	25

Discussion

There is no doubt that patients with infectious stones or a positive urine culture should be protected with antibiotic treatment during the ESWL procedure. Failure to do so might result in serious septicaemia or renal obstruction with infected urine and damage to renal function.

During ESWL it has been common practice to use a bladder catheter for diversion of urine during the diuresis that appears to be important for good distintegration, and to prevent voiding in the bath of those units where a water tub is used. We have also shown that ureteric catheters are of great value in a large number of patients (Pettersson and Tiselius, 1988). The administration of antibiotics has therefore tended to become a standard procedure in association with ESWL in many centres.

In this randomised study of non-infectious stones there was no difference in the rate of infectious complications between patients who were given antibiotics and those who were not, and the administration of methenamine hippurate did not appear to be of clinical value in this respect. It was somewhat surprising to find that the use of a ureteric catheter did not influence the occurrence of infection or bacteriuria. However, it needs to be emphasised that these catheters were usually removed immediately after treatment and since irrigation with saline was usually part of the therapeutic procedure, this might have contributed to the rapid elimination of bacteria if any were introduced with the catheter.

Although the number of patients differed slightly in the 3 groups, the size and location of the stones, ESWL types and results of treatment were similar. We are unable to explain the higher occurrence of infection among patients in Group B. Evidently the larger number of ureteric catheters used in this group was not responsible, and a more detailed analysis of the patients with infection failed to provide an answer. The higher frequency of large residual fragments among the patients in Group B thus could not be related to the occurrence of bacteriuria.

The principle underlying the action of methenamine hippurate is a conversion to formaldehyde in acid urine. No measurement of urinary pH was undertaken in these patients. However, when a separate group of patients was studied with regard to urinary pH during ESWL, 85% had a pH of 6 or more immediately after treatment and in 67% the pH was increased during the procedure. It is reasonable to assume that the high urine flow brought about by the routine administration of frusemide did result in a urine which was insufficiently acid to accomplish this conversion, particularly during the day of ESWL treatment. Thus Groups B and C should probably be considered together as being without treatment and, when doing so, this combined antibiotic-free group did not differ significantly from Group A with respect to infectious complications.

In addition to the high flow rate brought about by the diuretic regimen, the saline irrigation in patients with a ureteric catheter might have contributed to the low rate of infection in our patients.

As a result of these findings we have abandoned the routine administration of antibiotics to patients admitted for ESWL. Antibiotics were given only to patients with a positive bacterial dip-test, a positive culture, a recent history of urinary tract infection, the presence of a staghorn stone, or when there were other indications that the stone might be of infectious origin or associated with bacteria. Further more, prophylactic antibiotics were given to all patients with a percutaneous nephrostomy. All other patients underwent ESWL without antibiotics.

In a separate analysis of 77 consecutive patients treated at our ESWL unit according to these principles, antibiotics were considered necessary in 8 cases (10%). In the remaining patients, 2 (3%) required some form of treatment with antibiotics during the first 4 weeks after ESWL, a figure which is encouraging and supports the proposed regimen. It also needs to be emphasised that some patients might have fever caused by obstructing fragments not necessarily associated with infection.

In conclusion, the results in these randomly treated patients indicate that in a majority of renal stone formers prophylactic treatment with antibiotics is not necessary. This is of great advantage both from the medical and the economic point of view.

Acknowledgements

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Preliminary Nephrostomy and Total Ileal Replacement of both Ureters in Advanced Bilharzial Obstructive Uropathy

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Summary—Total substitution of both ureters in 5 patients with advanced obstructive uropathy due to extensive ureteric bilharziasis is described. It is recommended that ureteric replacement in the presence of marked obstructive uropathy should not be undertaken without preliminary renal drainage. An open through-and-through nephrostomy is recommended for this purpose. It is suggested that this approach will help to minimise the incidence of nephrectomy in areas of endemic urinary bilharziasis.

A significant degree of morbidity and mortality in urinary bilharziasis is related to involvement of the ureters. Segmental ureteric replacement by an ileal loop is a common surgical procedure in selected cases with this disorder (Honey and Gelfand, 1960; Abdel-Halim, 1980) but total ureteric replacement is unusual, since only rarely is the entire ureter affected. This report describes total ileal substitution of both ureters in 5 patients with advanced obstructive uropathy due to extensive ureteric bilharziasis.

Patients and Methods

Five Zambian males with an average age of 37 years (range 32–40) were managed by this method. All complained of tiredness, backache and intermittent passage of "white" urine for a minimum of 6 months. The only significant physical finding was tenderness over both loins. The investigations included haemoglobin, urea, creatinine, culture of midstream urine, cystoscopy and intravenous urograms with delayed films (Table). All urograms depicted the most severe form of bilateral hydronephrosis without any visualisation of the ureters (Figs 1 and 2).

Under an appropriate antibiotic cover a through-and-through type of open nephrostomy was performed on the most affected kidney. The procedure was repeated on the other kidney 2 weeks later. The subsequent investigations included antegrade ureterograms which invariably demonstrated multiple strictures extending from the vesicoureteric junction to the renal pelvis on both sides, often with associated tortuosity (Fig. 3). A repeat cystoscopic examination was also performed; patients with reduced bladder capacity were considered unsuitable for ileal ureters.

The ureteric replacement was undertaken within 6 months (but no earlier than 12 weeks) after nephrostomy. All patients received 1 course of schistosomicidal therapy shortly after renal drainage and another dose at the time of discharge.

Technique

Nephrostomy (Fig. 4). The kidney was exposed through a loin incision with excision of the twelfth rib. The incision in the renal pelvis was horizontal and in close proximity to the caliceal necks; such an incision did not interfere with the subsequent ileal anastomosis. The drainage tube was passed through the parenchyma overlying the upper and lowermost calices.

Ileal ureter (Fig. 5). A midline incision extending from the xiphisternum to the symphysis pubis

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Table Details of Patients

		Urea and creatinine					
No.	*Age (years)*	*Pre-op.*	*Post-op.*	*Urine culture*	*Hb.*	*Straight abdominal X-rays*	*Follow-up (years)*
1 (A.Z)	40	15 350	10 200	*E. coli*	10	No calcification	6
2 (S.S.)	32	11 215	9 200	*E. coli*	11	No calcification	2
3 (S.C.)	40	6 100	6 100	Sterile	13	No calcification	5
4 (A.C.)	35	22 548	12 300	*Pseudomonas*	12	No calcification	2
5 (G.K.)	39	12 250	9 200	*E. coli*	9.5	No calcification	3

provided the most satisfactory exposure. The anastomosis was always iso-peristaltic in direction; the distal end of the loop was everted to form a nipple and anastomosed to the bladder through a circular window. Each anastomosis was separately splinted and was brought out through the bladder and abdominal wall.

Results

All patients experienced a feeling of wellbeing within a few days of the first nephrostomy. A marked improvement in hydronephrosis and renal function was observed in all within 3 months of initiating renal drainage. Their recovery following ileal replacement was uneventful. The biochemical and radiological improvements (Figs 1 and 2) were sustained throughout the entire follow-up, which averaged more than 3 years (range 2–6). There was no evidence of electrolyte imbalance due to ileal absorption. All patients complained of mucus in the urine for up to 2 years.

Discussion

These results demonstate the effectiveness of total

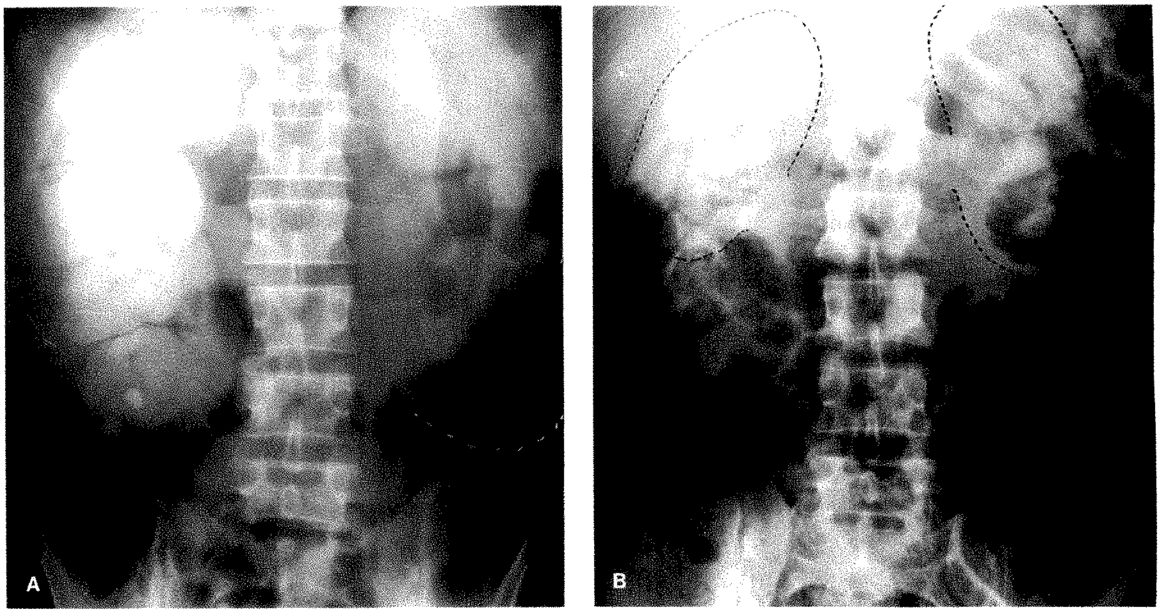

Fig. 1 (A) Case 1. Pre-operative urogram. Severe hydronephrosis without visible ureteric outlines after 5 h. (B) Sustained improvement in hydronephrosis 6 years after replacement of both ureters. No visible dilatation of the ileal segment.

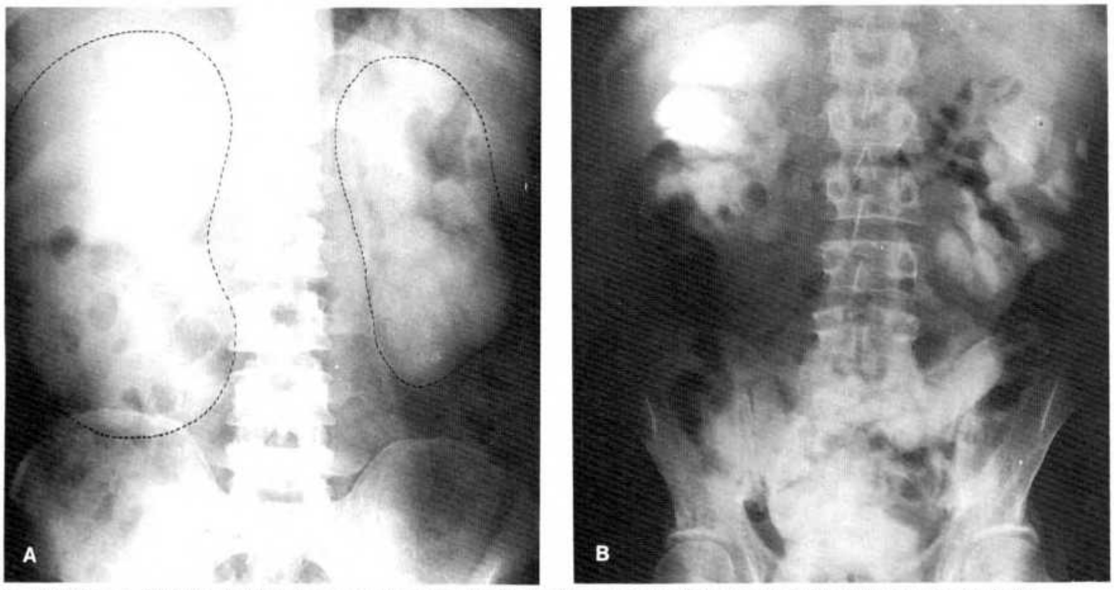

Fig. 2 (A) Case 5. IVU (24-h film) demonstrating severe obstructive uropathy. (B) Urograms $2\frac{1}{4}$ years post-operatively.

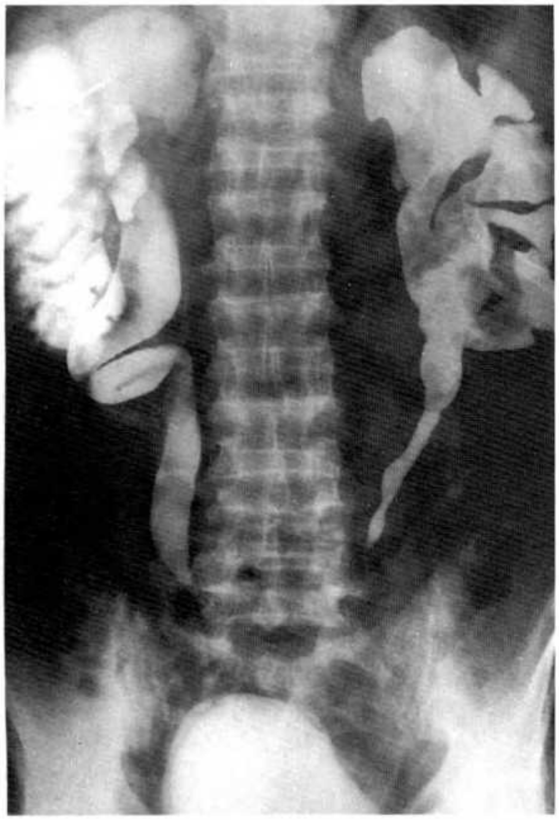

Fig. 3 Case 1. Antegrade pyelo-ureterogram through the nephrostomy tube showing multiple bilateral ureteric strictures and tortuosity on the right side.

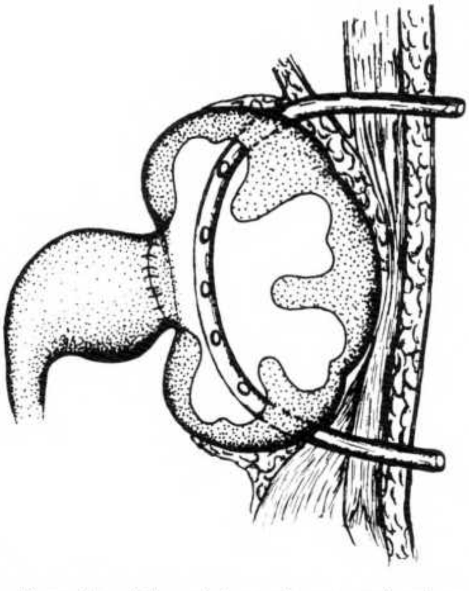

Fig. 4 Through-and-through type of open nephrostomy. The drainage tube (segment of a No. 18 Gibbon catheter) traverses the upper and lowermost calices. Dotted line indicates horizontal and high pelvic incision.

ureteric replacement by ileum in urinary bilharziasis. The uncomplicated recovery of all patients in the face of advanced bilateral obstructive uropathy was probably due to prolonged preoperative renal decompression. It seems certain that the reported mortality (Weinberg, 1970) and

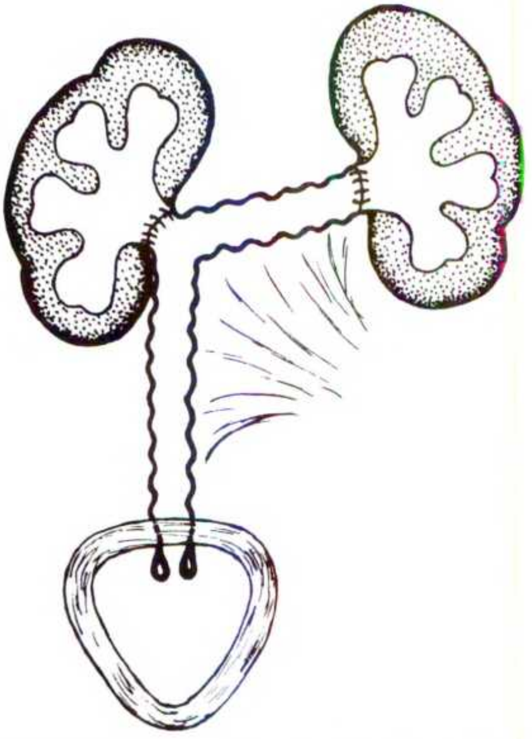

Fig. 5 Ileal ureter with end-to-end anastomosis on the left; intravesical ileal nipple.

poor urographic improvement of hydronephrosis (Amin, 1976) following ileal replacement of bilharzial ureters resulted either from inadequate or absent pre-operative drainage of the affected kidneys. Compared with present-day percutaneous nephrostomy, the open variety used here provided better drainage of the enormously dilated pelvicaliceal system.

Ileal replacement of the ureters should not be undertaken before the affected kidneys have been decompressed for at least 3 months. These patients need not be kept in hospital throughout this period, however, as the wide margin of safety against accidental removal of the drainage tube, and the ease of care of this type of nephrostomy, allow them to be followed up as out-patients.

It is suggested that in an area of endemic bilharziasis the above approach is likely to help in renal conservation in situations where nephrectomy would otherwise seem inevitable.

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Renal Carcinomas Missed by Urography

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Summary—It is well accepted that renal masses are missed on intravenous urography. We present 3 patients with renal carcinoma; their tumours, measuring between 3 and 5 cm, were not detected on good quality IVU but were demonstrated on ultrasound. We wish to emphasise the importance of performing an ultrasound or computed tomography examination in cases where a renal tumour is suspected when the IVU is normal.

Unsuspected renal cysts are frequently discovered even when the IVU is normal. During a 6-month period we detected sonographically 13 simple cysts larger than 2 cm which had not been detected on IVU. This raised the question of how many renal carcinomas are being missed on IVU. A retrospective study was performed to compare the results of intravenous urography, ultrasound and computed tomography to establish how many cases had been missed.

Patients and Methods

Over a 3-year period, 62 cases of renal carcinoma were confirmed histologically in the Grampian Region; 3 of these patients were found to have had a normal IVU. In each case the tumour was demonstrated on ultrasound and in 1 case on computed tomography. Good quality IVUs were performed with nephrotomograms where appropriate. Ultrasound examinations were performed on commercially available real time sector scanners, using a 3.5 MHz transducer. Computed tomography was performed on a third generation scanner.

Results

Case 1. A 78-year-old man presented with haematuria and passage of blood clots. Clinical examination was normal. Bladder was normal at cystoscopy. IVU demonstrated a mass at the lower pole of the left kidney (Fig. 1), otherwise normal. Ultrasound confirmed this to be a simple 6-cm multiloculated cyst. In addition a 3-cm rounded solid mass arising from the posterior aspect of the lower pole of the right kidney was demonstrated (Fig. 2). CT scan confirmed this solid mass.

The right kidney was explored and a 3-cm carcinoma confirmed at histology. There was no extracapsular spread. Unfortunately, this patient now has cerebral metastases.

Case 2. A 69-year-old man was admitted to hospital with a CVA. He made a good recovery but developed right upper quadrant pain. On examination he was tender in

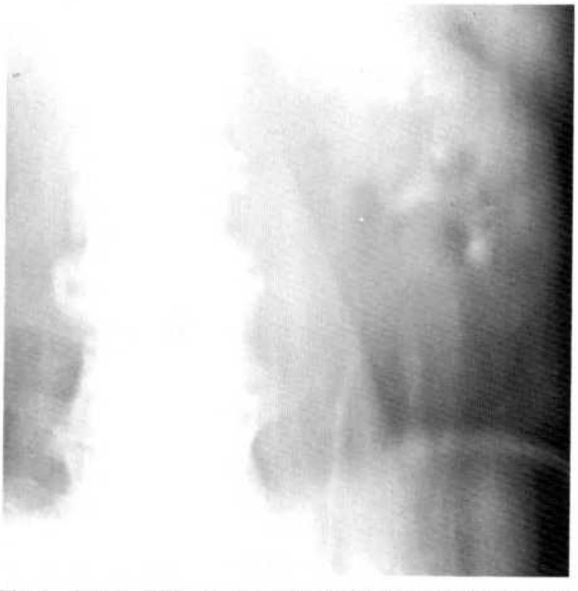

Fig. 1 Case 1. IVU, tomogram at 15 min. Cyst projecting from the lower pole of the left kidney, normal right kidney.

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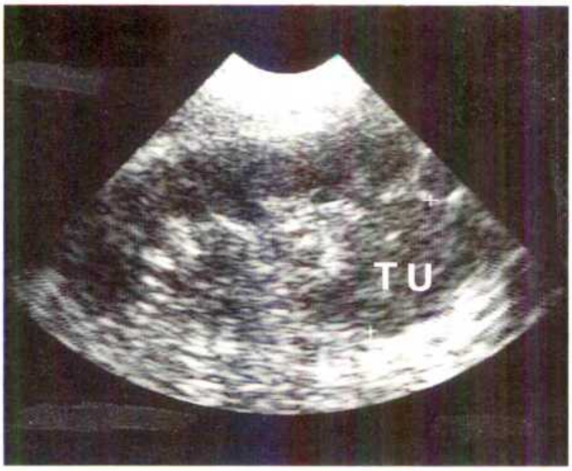

Fig. 2 Case 1. Coronal longitudinal US right kidney. Lower pole solid mass 3 cm in diameter. TU = Tumour.

the right hypochondrium, otherwise normal. Ultrasound showed a 3.5-cm solid mass in the anterior aspect of the lower pole of the right kidney (Fig. 3). IVU was normal.

The right kidney was explored and a 4-cm carcinoma was confirmed histologically. There was no extracapsular disease.

Case 3. A 69-year-old male presented with prostatism. He had benign prostatic hypertrophy but was otherwise normal. IVU demonstrated a mass at the lower pole of the right kidney (Fig. 4) and evidence of prostatic enlargement. Ultrasound showed the right lower pole mass to be a simple cyst; in addition there was a 5-cm solid mass in the anterior aspect of the upper pole of the left kidney (Fig. 5).

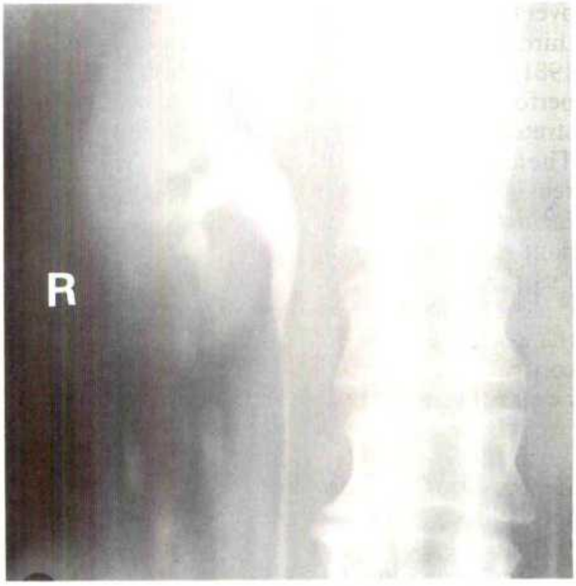

Fig. 4 Case 3. IVU, tomogram at 15 min. Normal left kidney. Cyst projecting from the lower pole of the right kidney.

At operation a 5-cm haemorrhagic renal carcinoma was removed with no extracapsular spread.

Discussion

Renal masses are very common. At autopsy 55% of the population over 50 years of age have at least one simple cyst (Kissane, 1974). In the population

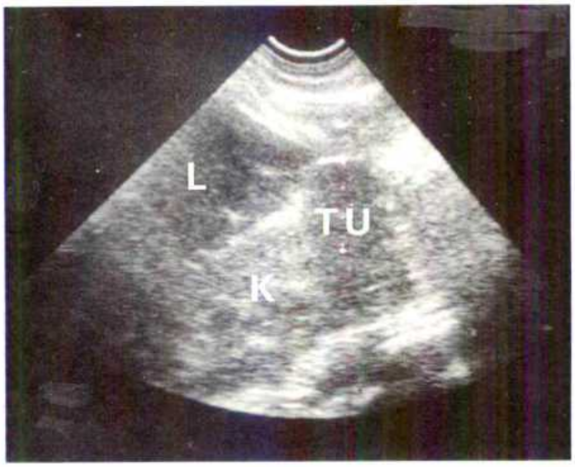

Fig. 3 Case 2. Sagittal longitudinal US right kidney demonstrating an anterior lower pole mass 3.5 cm in diameter. L = Liver. TU = Tumour. K = Kidney.

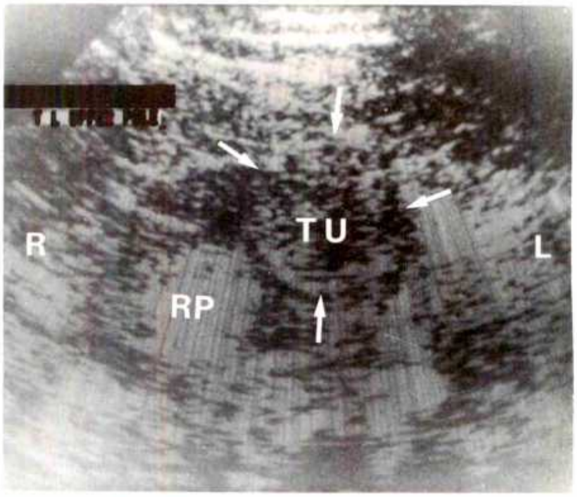

Fig. 5 Case 3. Transverse US left kidney demonstrating an anterior solid mass 5 cm in diameter. RP = Renal pelvis. TU = Tumour.

over the age of 60 years cysts were identified in one-third of patients on CT (Laucks and McLachlan, 1981). In a similar age group, however, IVUs performed in patients with prostatism demonstrated renal masses in only 15% (Lang, 1973). These studies suggest that approximately 15% of renal masses are being missed on IVU; 5 to 10% of incidental masses demonstrated on IVU are malignant (Livingston *et al.*, 1981). We can infer from this that the same percentage of lesions that are missed on IVU will also be malignant. Following the work of Bell in 1947 it was suggested that renal cortical tumours less than 3 cm in diameter could be classified as benign cortical adenomas. This has been challenged, especially during the past 10 years, partly because of more reported cases of renal tumours less than 3 cm in diameter with associated metastases (Amendola *et al.*, 1988). This emphasises the importance of not missing these small lesions.

Renal carcinoma has an overall incidence of 5.6/100,000 (Dayal and Kinman, 1983). We would expect to see approximately 66 cases over a 3-year period in Grampian. Our study showed that 62 cases actually occurred, 3 of which were missed on IVU, confirming the generally accepted prediction that 5 to 10% of renal tumours are missed on this examination.

Renal masses are missed for a number of reasons. It is generally accepted in the literature that tumours located on the anterior or posterior surface of the kidney may not distort the renal outline or the caliceal system. Small masses in any position may also be missed. In 2 of our patients the tumour was found on the anterior and in 1 on the posterior aspect of either the upper or lower pole of the kidney. The average size of tumours at presentation is 7.5 cm (Bennington and Kradjian, 1967). In all 3 of our cases the tumours were less than 5 cm in diameter. Lesions over 2 cm in size are detectable by ultrasound.

The importance of tomography should not be underestimated as it has been demonstrated that this increases the pick-up rate of incidental masses. However, despite tomography being included in the IVU, 5 to 10% of lesions are still missed.

CT is considered best at the staging of renal tumours (Zenman *et al.*, 1985). In a recent study of small renal carcinomas less than 3 cm in diameter, it was found that computed tomography had a sensitivity of 94% compared with ultrasound (79%) and IVU (67%) (Amendola *et al.*, 1988). However, ultrasound is more readily available than CT, is less expensive and does not involve ionising radiation. Ultrasound can detect all large renal tumours and the majority of tumours less than 3 cm in size. It should be used in the first instance to establish the diagnosis and is excellent at detecting extracapsular spread and venous involvement.

Classically, a renal tumour presents with loin pain, haematuria and a palpable mass. In these cases the tumour is large and the diagnosis is usually made on IVU. However, these signs may be entirely absent and more non-specific signs present such as fever or anaemia. The patient may present with clinical manifestations of a secondary deposit or the tumour may be entirely silent. In situations where the IVU is negative we recommend that an ultrasound examination be performed in the first instance. CT scan should be performed in those cases where the initial investigations have been negative but where the suspicion of renal carcinoma exists.

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Contemporary Flow Meters: an Assessment of their Accuracy and Reliability

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Summary—The accuracy, reliability and cost effectiveness of 5 currently marketed flow meters have been assessed. The mechanics of each meter is briefly described in relation to its accuracy and robustness. The merits and faults of the meters are discussed and the important features of flow measurements that need to be taken into account when making diagnostic interpretations are emphasised.

Estimation of the urinary flow rate is an essential investigation in routine urological practice (Drake, 1948). Without this simple test an objective diagnosis of outflow obstruction cannot be made. The importance of this investigation has also been appreciated in the commercial sector and a wide range of equipment is now available. The aim of this study was to assess the cost effectiveness, accuracy and reliability of the principal flow meter designs currently marketed in the UK.

Methods

Each meter was tested twice using apparatus which delivered a constant flow rate (20 ml/s) over a precisely determined volume (400 ml). The flow meters tested were display models which were in optimum functional order and had been accurately calibrated by the manufacturers. The percentage error in the estimation of maximum flow rate and recorded volume was calculated for each device. The long-term reliability of each apparatus, except the F.M. Wiest meter, was assessed in the urodynamic units run by our department. The cost of each flow meter was determined by application to each manufacturer.

Results and Discussion

Estimation of the maximum urinary flow rate revealed an error of between 4.5 and 15% which was consistent on repeated testing of that particular model (Table 1). The error in the recording of volume ranged between 1.3 and 7.5% (Table 2). The Dantec apparatus appeared to be the most accurate, but difficult to clean if soiled by solid material, and it had the disadvantage that because it uses a spinning wheel mechanism the readings altered when testing material of different density

Table 1 Accuracy in Measuring Flow Rate (20 ml/s)

	Error (%)
Dantec	4.5
Gaeltec	5.0
Micromedics	5.0
Lectromed	10.0
F. M. Wiest	15.0

Table 2 Accuracy in Recording Volume (400 ml)

	Error (%)
Dantec	1.3
Lectromed	2.5
Gaeltec	3.8
Micromedics	6.7
F. M. Wiest	7.5

Based on a Poster Demonstration at the 44th Annual Meeting of the British Association of Urological Surgeons in Buxton, June 1988 from that of urine (*e.g.* contrast medium after videocystometrography). The Lectromed and Micromedics meters use a dipstick principle which has the advantage of being less complex and reasonably accurate. Unfortunately these dipsticks are highly susceptible to mechanical damage and suffer from the fundamental methodological drawback that leads to significant artefacts produced by turbulence within the measured fluid. This problem has to some extent been overcome by incorporation of an anti-wave barrier in the most recent models. However, this damping procedure may suppress authentic fluctuations in the flow rate and pattern. The Gaeltec and F.M. Wiest devices work using pressure transducers which enable the collection equipment to be more easily cleaned. The Gaeltec apparatus was very accurate and robust and produced a colour printout incorporating a voided volume graph. The F.M. Wiest flow meter was expensive and the most inaccurate in the measurement of flow rate and voided volume. The relative costs of the meters are shown in Table 3.

Long-term assessment of the sturdiness and reliability of all of the meters (except the Wiest) demonstrated little difference. A single Micromedics machine was prone to printer failure, as was a Gaeltec, and 1 of 4 Dantec meters developed a fault in the spinning wheel mechanism. In all cases repairs were performed within 48 h, although we cannot be sure that such a good service would be available outside a major city.

In the practical context we believe that reliability is the most important consideration when choosing a flow meter. Errors of up to 15% are acceptable, since single flow rate values are not in themselves absolutely diagnostic. The interpretation of voiding recordings depends upon the average and maximum flow rates and the flow pattern; integration of these independent variables should enable the investigator to reach a diagnosis. In addition, however accurate the measurement of flow rate, the influence of factors such as the initial bladder volume, and therefore also the post-micturition residual (Siroky *et al.*, 1979), and the effects of abdominal straining (Christmas *et al.*, 1988) need to be taken into consideration.

In our experience of the clinical use of all of the meters, except that produced by F.M. Wiest, the Dantec appeared the most reliable and robust.

Table 3 Cost of Apparatus in the UK (May 1988)

	£ (excluding VAT)
Micromedics	950 (excluding commode)
Lectromed	1550
Gaeltec	1700
Dantec	1990
F. M Wiest	2700

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Non-functioning Tumours of the Adrenal Cortex

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Summary—Twelve cases of non-functioning adrenal tumours are presented. All were discovered incidentally during radiological investigation of abdominal conditions or staging of known malignancies. Adrenal tumours in patients with known malignancies are not necessarily metastases. Size remains the most important factor in determining their management and tumours larger than 3.5 cm should be operated on because of the possibility of malignancy. Smaller tumours should be assessed by computed tomography (CT) every 3 months for 1 year. Any change in contour, margin, density or hormone function during the follow-up period indicates the need for surgery.

As computed tomography and ultrasonography are used widely in the diagnosis of abdominal conditions, increasing numbers of unexpected asymptomatic adrenal masses are discovered. The frequency of these tumours ranges from 0.6 to 0.7% of the total number of CT studies (Glazer *et al.*, 1982; Belldegrun *et al.*, 1986). The significance and management of these masses have also been discussed and we report our experience.

Patients and Methods

All patients with adrenal tumours seen between 1979 and 1987 were reviewed. Each patient received all or some of the following endocrine studies: urinary 17-ketosteroid, 17-hydroxycorticosteroid, vanillylmandelic acid, catecholamine, plasma cortisol, aldosterone, epinephrine or norepinephrine. Patients with clinical or biochemical evidence of abnormal hormone production were excluded, as were those with adrenal cysts, myelolipomas and tumours of the adrenal medulla, whether functioning or non-functioning. Twelve cases of non-functioning adrenal cortex tumours were seen during this period. All were found incidentally by intravenous urography, abdominal sonography or computed tomography as a result of diagnosing abdominal conditions or staging of a known malignancy.

Results

The clinical features of these 12 patients are shown in the Table.

Five of the 12 adrenal tumours were malignant in nature, 2 being adrenal corticocarcinomas (cases 2 and 5). Both tumours were large, with irregular contours and uneven attenuation on computed tomography. In only 1 patient (case 2) was calcification found inside the tumour. Case 9 was found to have a malignant lymphoma post-operatively. Since further evaluation failed to reveal any lesion, primary lymphoma of the adrenal gland was suspected. Cases 3 and 11 had metastatic adenocarcinomas but the primary lesions were not found. The contours of these 3 adrenal masses were smooth and attenuation was even. The relatively large size of the tumours indicated the need for surgery.

Case 4 was admitted for evaluation of hypertension at a relatively young age (28 years). She had a 1.5-cm tumour over the right adrenal gland. Surgery was performed, although the endocrine studies were all within normal limits. Hypertension persisted post-operatively and she was found to have a cortical adenoma.

A further 5 patients did not receive surgery but were followed up by CT scans. Cases 10 and 12 received abdominal CT as part of the staging of their known malignancies. The adrenal mass in case 10 was missed on CT before nephroureterectomy and the patient refused a second operation to

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Table Clinical Features

Case No.	*Age (years)*	*Sex*	*Reasons for radiological evaluation*	*Endocrine studies*	*Site*	*Size (cm) (maximum diameter)*	*Pathology*	*Follow-up*
1	43	M	Abdominal pain	Normal	Rt	2.5	—	No change 2 years later
2	20	M	Abdominal mass	Normal	Lt	20	Cortical carcinoma	Died 1 year after surgery
3	73	M	Abdominal pain	Normal	Rt	4	Metastatic adenocarcinoma	Origin unknown until death
4	28	F	Hypertension	Normal	Rt	1.5	Adenoma	Hypertension persisted after surgery
5	51	M	Abdominal mass	Normal	Rt	6	Cortical carcinoma	Survival 5 years after surgery and radiotherapy
6	62	M	Constipation	Normal	Rt	3	—	No change 1 year later
7	63	F	Flank pain	Normal	Rt	3.5	Adenoma	—
8	58	F	Abdominal pain	Normal	Lt	3	—	No change 1 year later
9	68	F	Abdominal pain	Normal	Lt	4	Lymphoma	Chemotherapy, survival
10	61	M	Transitional cell carcinoma of left ureter	Normal	Lt	2	—	No change 6 months later
11	57	M	Abdominal pain	Normal	Lt	4.5	Metastatic adenocarcinoma	Origin unknown, survival
12	63	M	Left renal carcinoma	Normal	Rt	1	—	No change 3 months later

remove this ipsilateral adrenal tumour. Follow-up CT 6 months later showed no change in size or contour of the tumour. Case 12 was found to have a small adrenal mass when his renal carcinoma was diagnosed. Since the mass was small, surgery was not indicated and follow-up CT 3 months later showed no change in the tumour.

Discussion

Computed tomography has been one of the most frequently used methods of diagnosing abdominal conditions and its ability to identify the adrenal gland has also been confirmed. Thus previously unsuspected adrenal tumours have been found in increasing numbers and several factors have been emphasised in their evaluation and management. Most workers agree that complete endocrine studies should be performed on all patients and functioning adrenal tumours should be treated surgically (Prinz *et al.*, 1982; Guerrero, 1985).

In the case of non-functioning adrenal tumours, radiological criteria are important. In general, a smooth contour and well delineated margin indicate benign adenoma. Punctate calcification and varying densities are more common in carcinoma but have also been seen in benign lesions (Mitnick *et al.*, 1983). Our findings confirm these observations.

Age has also been mentioned as a consideration. Since adrenal carcinomas are less likely in older patients, Prinz *et al.* (1982) and Guerrero (1985) suggested that patients over the age of 50 or 60 years should be treated conservatively. The 2 patients with adrenal corticocarcinomas in the present series were aged 20 and 51 years at the time of surgery. However, the 3 patients with metastatic adenocarcinoma and lymphoma were 57, 73 and 68 years old. Thus age alone may not be a reliable factor in determining the nature of the adrenal tumour.

A higher incidence of non-functioning adenomas has been reported in patients with some malignancies, especially those of the urinary bladder, endometrium and kidney (Parker and Sommers, 1956; Ambos *et al.*, 1981) and adrenal tumours in these patients are not necessarily metastases. These adrenal masses should be treated in the same way as the other incidental adrenal tumours. Cases 10 and 12 in this series provide support for this suggestion.

Several reports have mentioned size as the most important factor. In general, the larger the tumour the more likely it is to be malignant. Various proposals, ranging from operating on all adrenal tumours to restricting surgery to tumours larger than 6 cm, have been put forward (Glazer *et al.*, 1982; Prinz *et al.*, 1982; Copeland, 1983; Mitnick *et al.*, 1983; Guerrero, 1985, Seddon *et al.*, 1985; Belldegrun *et al.*, 1986). At autopsy, however, the adrenal glands have been found to contain macroscopic non-functioning adenomas in 1.45 to 33% of adult patients (Russi *et al.*, 1945). In the present series, tumours measuring less than 3.5 cm were all benign. Thus it is concluded that any adrenal tumour exceeding 3.5 cm requires surgery. However, bearing in mind the fact that large malignant adrenal tumours can develop from much smaller lesions, even small tumours should be followed up by CT scans every 3 months for 1 year. The tumour should be excised if there is any change in size, contour, attenuation or hormone function during this time.

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Transvesical Phenol Injection of Pelvic Nerve Plexuses in Females with Refractory Urge Incontinence

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Summary—A series of 28 female patients with urge incontinence refractory to other forms of treatment underwent a total of 40 transvesical injections of phenol into the pelvic nerve plexuses. Following primary phenol injection only 8 patients (29%) had a significant response to therapy and all relapsed during follow-up. Only 3 of 11 patients undergoing a second injection had a clinical response to this therapy and 1 developed a vesicovaginal fistula. This suggests that phenol injections have little place in the management of urge incontinence and it is unwise to proceed to 2 or more injections because of the risk of fistula.

The management of frequency, urgency, urge incontinence and nocturia in women with unstable or hypersensitive bladders continues to be a distressing clinical problem. Patients with sensory urgency or mild idiopathic detrusor instability are often successfully managed with intensive bladder re-training (Frewen, 1978; Jarvis, 1982). If this fails, or if the patient has a neuropathic cause for her symptoms, several pharmacological treatments are available, the most useful being propantheline bromide (Blaivas *et al.*, 1980), imipramine (Cole and Fried, 1972), terodiline hydrochloride (Ulmsten *et al.*, 1985) or oxybutynin hydrochloride (Moisey *et al.*, 1980). Unfortunately, many patients find that these drugs are either ineffective or the side effects are intolerable. Pharmacological treatment having failed, patients with severe symptoms are often left with no alternative but major surgery. The surgical options include transvaginal bladder denervation (Ingelman-Sundberg, 1978), selective sacral neurectomy (Lucas *et al.*, 1988), bladder transection (Mundy, 1982) or augmentation cystoplasty (Mundy and Stephenson, 1985). The technique of transvesical injection of phenol into the pelvic nerve plexuses has been described by Ewing *et al.* (1982). If effective, this appears to be a simple and much less traumatic technique for the treatment of the unstable bladder and related disorders.

Patients and Methods

Between December 1983 and November 1987, 28 women aged 19 to 75 years (mean 52) underwent a total of 40 transvesical phenol injections. Urodynamic diagnoses (Table 1) were made using dual channel subtracted cystometry with or without videocystourethrography. All terms and definitions conform to the recommendations of the International Continence Society (Bates *et al.*, 1976). The neurological diagnoses of patients with detrusor hyper-reflexia are shown in Table 2. All patients undergoing phenol injection had not responded to prior therapy (average number of previous failed therapies was 4).

The technique used for injection has been previously described (Murray *et al.*, 1986). Under general anaesthesia the patients underwent cytoscopy and a needle 35 cm in length was passed

Table 1 Diagnoses

Detrusor hyper-reflexia	7
Detrusor hyper-reflexia and genuine stress incontinence	1
Idiopathic detrusor instability	9
Idiopathic detrusor instability and genuine stress incontinence	6
Low compliant bladder and genuine stress incontinence	3
Nocturnal enuresis and genuine stress incontinence	1
Sensory urgency	1
Total	28

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Table 2 Neuropathic Aetiology of Detrusor Hyper-reflexia

Spina bifida	2
Cerebral palsy	1
Neurofibromatosis	1
Multiple sclerosis	2
Transverse myelitis	1
Cerebrovascular accident during post-partum eclamptic seizure	1
Total	8

through the bladder wall to a depth of 2 cm halfway between the bladder neck and ureteric orifice on each side; 10 ml of 5% aqueous phenol were then injected bilaterally. The tip of the needle was palpated vaginally during the course of the procedure to ensure that it had not penetrated the vaginal wall. An indwelling Foley catheter was then left to drain freely overnight and removed the following morning. The patients were discharged when they were voiding spontaneously. They were seen for review 8 weeks after the injection and intermittently therafter, depending on their individual needs and clinical situations. Repeat cystometry was subsequently performed on 13 patients at varying intervals.

Results

Only 2 patients undergoing repeat cystometry reported any symptomatic improvement following phenol injection and objective urodynamic changes were not apparent in either case. Subjective improvement in symptomatology was graded into 3 categories of "no response", "slight response" and "significant response". After the initial phenol injection 16 patients (57%) had no response, 4 (14%) had a slight response and 8 (29%) had a significant subjective improvement in symptoms. Response by diagnostic category is given in Table 3. Eight of 15 patients with idiopathic detrusor instability showed some improvement, as did 4 of 8 patients with detrusor hyper-reflexia. None of the 3 patients with low complaint bladders noticed any improvement. Of 11 patients who had genuine stress incontinence as part of a diagnosis of mixed incontinence, only 2 showed any improvement.

The duration of response to primary phenol injection is given in Table 4. The average duration of significant response was 8.3 months (range 2–22) but all patients who had a response relapsed during the period of follow-up, which ranged from 6 months to 4 years.

The response to repeat phenol injections is shown in Table 5. Of 11 patients undergoing repeat procedures, only 3 reported any improvement and in 2 of these the response was short-lived. A third attempt at phenol injection was made in 1 patient, who had a significant response for 8 weeks; this then faded, although some improvement was still present 12 months later.

Three patients had complications from phenol injection; 1 developed significant haematuria with the passage of clots, which cleared spontaneously within 24 h. Another patient developed post-operative voiding difficulty which required the placement of a suprapubic catheter. Normal spontaneous voiding returned within 7 days, as did her uninhibited detrusor contractions and motor urge incontinence. A third patient who underwent a second injection of phenol developed a vesicovaginal fistula.

In general, all patients remain incontinent and unhappy, and many have subsequently gone on to major urological surgery in an attempt to improve the quality of life.

Table 3 Subjective Responses to Primary Phenolisation by Diagnostic Category

Diagnostic category	*No response*	*Slight response*	*Significant response*
Detrusor hyper-reflexia (n = 7)	4	1	2
Detrusor hyperreflexia and genuine stress incontinence (n = 1)	0	0	1
Idiopathic detrusor instability (n = 9)	3	3	3
Idiopathic detrusor instability and genuine stress incontinence (n = 6)	5	0	1
Low compliant bladder and genuine stress incontinence (n = 3)	3	0	0
Nocturnal enuresis and genuine stress incontinence (n = 1)	0	0	1
Sensory urgency (n = 1)	1	0	0
Total (n = 28)	16	4	8

Table 4 Duration of Subjective Responses to Primary Phenolisation

	No response (n = 16)	*Slight response (weeks) (n = 4)*	*Significant response (months) (n = 8)*
Average duration	—	4	8.3
Range	—	2–8	2–22

Table 5 Subjective Response to Repeat Phenol Injections

	No. of patients	*Duration of response*
Second injection	11	
No response	8	
Slight response	1	8 weeks
Significant response	2	1 for 8 weeks 1 for 12 weeks, with slight residual response at 9 months
Third injection	1	Significant response for 8 weeks, with slight residual response at 12 months

Discussion

Aqueous phenol has been shown to exert a powerful neurolytic effect (Parkhouse *et al.*, 1987). The technique of transvesical injection is an attempt to place this neurolytic agent into the pelvic nerve plexuses where they lie on the anterolateral vaginal wall beneath the bladder in the female (Mundy, 1982). While this technique is relatively atraumatic and easy to perform, it remains unpredictable in its clinical effects. Although some authors have reported good results in selected groups such as patients with multiple sclerosis (Ewing *et al.*, 1983), detrusor hyper-reflexia (Ewing *et al.*, 1982; Blackford *et al.*, 1984; Murray *et al.*, 1986) or older women with idiopathic detrusor instability (Blackford *et al.*, 1984), others have not been so successful (Nordling *et al.*, 1986). Unfortunately, our experience has been more in accord with this latter group.

In our hands, transvesical phenolisation appears to help only a minority of patients and does not produce a long-term cure of the symptoms of urgency, frequency, nocturia and urge incontinence associated with the unstable bladder. Patients with mixed incontinence, due to the presence of genuine stress incontinence in particular, appear to respond poorly to this therapy and would perhaps benefit from earlier surgery to correct their urethral sphinter incompetence.

Reported complications of phenol injection include superficial ulceration of the trigone (Ewing *et al.*, 1983), sciatic nerve palsy (Blackford *et al.*, 1984) and acute and chronic urinary retention (Cox and Worth, 1986; Nordling *et al.*, 1986). Perhaps of greater concern is the risk of fistula formation. In this series, attempts at repeat injection of phenol were not very successful and a vesicovaginal fistula appears in a patient undergoing a second injection. Nordling *et al.* (1986) also reported a vesicovaginal fistula occurring in a patient following a second phenol injection. We feel, therefore, that the marginal utility of repeat injections is small. Nonetheless, provided patients understand its unpredictability and low level of effectiveness, transvesical injection of the pelvic nerve plexuses with phenol may provide temporary relief to some patients with disabling urinary tract symptoms and is worth consideration prior to embarking on more extensive surgical treatment.

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The Value of Intravesical Echography Combined with Double-surface Coil Magnetic Resonance Imaging in Staging Bladder Cancer

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Summary—Correct staging of bladder tumours is essential for planning the best therapeutic strategy and is therefore directly related to the prognosis. In this study of 15 patients with bladder cancer, a new method using magnetic resonance imaging (MRI) with a newly developed double-surface coil was tested for bladder cancer staging and compared with other existing techniques.

Ultrasonography produced 2 cases of overstaging and 2 of understaging. This was due to the inability of this method to evaluate muscular infiltration accurately. All superficial bladder tumours were staged correctly with ultrasound with the exception of 1 case that was overstaged because of superficial tumour calcification. Double-surface coil MRI correctly staged all infiltrating tumours. Two small superficial tumours were missed by MRI, while another superficial tumour was overstaged.

It is suggested that double-surface coil MRI and intravesical ultrasonography are good complementary examinations in the pre-operative staging of bladder tumours. Larger studies are necessary to prove the reliability of this conclusion.

Correct tumour staging in patients with bladder carcinoma has always been essential both for planning treatment (Denis *et al.*, 1984; Denkhaus *et al.*, 1985; Debruyne and Hendrikx, 1988) and for the prognosis (Jewett and Strong, 1946; Marshall, 1952; Schmidbauer *et al.*, 1984). Three major treatment groups can be distinguished (Schmidbauer *et al.*, 1984):

1. pTa–1–is: transurethral resection ± intravesical instillation.
2. pT2–3a: diagnostic TUR with subsequent radical cystectomy (± neo-adjuvant chemotherapy or pre-operative radiation therapy).
3. pT3b–4: diagnostic TUR followed by radiation, cystectomy or chemotherapy, especially if lymph node involvement or distant metastasis is established.

Although new diagnostic methods (*e.g.* flowcytometry, tumour antigens) are gaining greater currency, tumour grading and staging are still important in day-to-day clinical practice.

Several diagnostic methods are available to determine how deep a bladder tumour has infiltrated, but most of them fail to predict correctly the final pathological staging. Using clinical examination, including bimanual (transrectal or vaginal) palpation, IVU and urethrocystoscopy, staging errors can be present in more than 40% of cases (Prout, 1982) and in a review by Jaeger *et al.* (1986) range from 0 to 79%. If bimanual examination is performed under anaesthesia, slightly better results can be obtained (Engelmann *et al.*, 1984). With the help of the CT scan, staging the extent of the disease can be further improved (Engelmann *et al.* 1984; Arger, 1985; Barentz *et al.*, 1988).

The introduction of intravesical ultrasonography and, more recently, of double-surface coil MRI have also improved the accuracy of pre-operative staging of bladder tumours (Cummings, 1982;

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Denis *et al.*, 1984; Jaeger *et al.*, 1986; Barentz *et al.*, 1988). In this study the different diagnostic methods are compared and evaluated.

Patients and Methods

Fifteen patients with newly diagnosed bladder tumours were examined prospectively by 6 different investigators, each using a different diagnostic procedure (D1–D6) in order to stage the tumour.

D1 consisted of clinical investigation, including transrectal or vaginal examination, intravenous urography (IVU) and urethrocystoscopy (UCS). After this procedure, the first diagnosis was defined according to the criteria described by the UICC (1978). The second diagnostic procedure (D2) consisted of MRI using a double-surface coil in a Philips superconducting unit (Gyroscan S5) operating at a field strength of 0.5 Tesla as described by Barentz *et al.* (1988).

The third diagnostic procedure (D3) was a CT scan, which was applied in only 5 patients with a bladder tumour suspected of invasion. D4 consisted of the same procedure as D1, but bimanual palpation of the tumour was carried out under regional or general anaesthesia. This bimanual examination was performed before and after resection.

The fifth diagnostic technique (D5) applied to all patients and employed intravesical ultrasonography with a Brüel and Kjaer instrument. Finally, the diagnosis (D6) was established by pathological examination of the differentiated resected bladder tumour and the cold random biopsies. Again, the staging criteria of the UICC (1978) were used. All diagnostic steps (D1–D6) were compared and instances of over- and under-staging were recorded. Initially we intended to study 19 patients. In 2 patients the ultrasonic imaging was not successful because of tumour bleeding and blood clots, which disturbed the image; 2 patients could not undergo MRI in time. Thus the results of only 15 patients (10 male, 5 female) could be included in this report. Their ages varied from 33 to 77 years (mean 59).

Results

The details of the 15 patients are shown in Table 1. None of the patients with a pT2–3 tumour could undergo a cystectomy, in 4 cases positive lymph nodes were found, in 1 case a benign tumour of the Wolffian duct was diagnosed (Fig. 1), while another patient was unfit.

Table 1 Details of Patients (Lymph node staging was established by lymphography and pathological examination of pelvic lymph nodes or puncture material. Staging of metastases was established by tomography of the thorax and CT scanning of the abdomen.)

	Sex	*Age*	*Final diagnosis*	*Mucosal biopsies*	*Therapy*
1	F	65	CIS NxMx	CIS	II[1]
2	M	60	pTa G1 NxMx	NAD	II
3	M	40	pTa G1 NxMx	NAD	II
4	M	67	pTa G1–2 NxMx	NAD	II
5	M	65	pTa G1 NxMx	NAD	II
6	M	76	pT3b G3 N0M0	NAD	RT[2]
7	F	75	pT3a G3 N1M0	NAD	RT
8	M	54	pT2 G3 N4M0	NAD	RT
9	M	37	pT1 NxMx	NAD	RT
10	F	73	pTa G1 NxMx	NAD	II
11	M	77	pTa G2 NxMx	NAD	UCS[3]
12	M	51	pT3b G3 N4M0	NAD	MVAC[4]
13	M	69	pTa G2 NxMx	NAD	II
14	F	42	pTa G2 NxMx	NAD	II
15	F	33	Pt4a Tumour of Wolffian duct, mucosa intact		UCS

[1] II: Intravesical instillation of MMC or BCG.

[2] RT: Radiotherapy.

[3] 3-monthly as a control: urethrocystoscopy.

[4] Intravenous chemotherapy with mitomycin, vinblastine, Adriamycin and cisplatin.

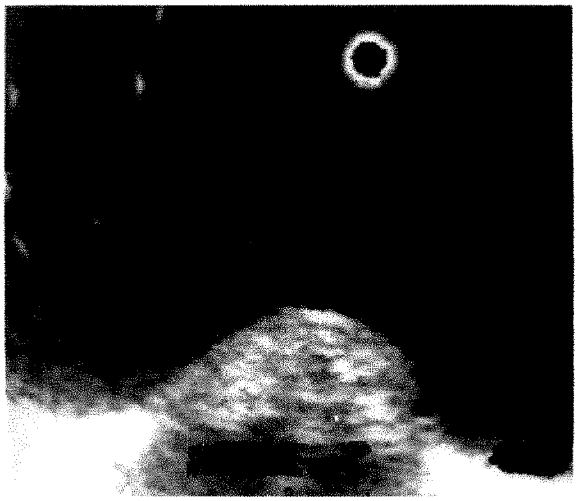

Fig. 1 Case 15. Intravesical ultrasound (5.5 MHz) showing tumour under trigone, which is elevating intact bladder mucosa. The tumour itself penetrates bladder muscle (2 cm per division).

From Table 2 it can be seen that with ultrasonography correct staging was obtained in 11 patients; 2 were understaged and 2 were overstaged; 3 of the 4 cases of incorrect staging were in the group with invasive bladder tumours. Superficial bladder car-

Table 2 Comparison between Ultrasonography and Pathological Stage

	D5 (US)	*D6 (PA)*	*C/O/U*[1]
1	Ta–1	CIS	˜C
2	Ta–1	pTa	˜C
3	Ta–1	pTa	˜C
4	Ta–1	pTa	˜C
5	Ta–1	pTa	˜C
6	T2–3a	pT3b	U
7	T3b–4	pT3a	O
8	T2–3a	pT2	˜C
9	T2–3a	pT1	O
10	Ta–1	pTa	˜C
11	Ta–1	pTa	˜C
12	T2–3a	pT3b	U
13	Ta–1	pTa	˜C
14	Ta–1	pTa	˜C
15	T3b–4	pT4a	˜C

[1] C: Correct staging
˜C: Almost correct staging, difference is without therapeutic consequences
O: Overstaging
U: Understaging

Table 3 Comparison between MRI and Pathological Stage

	D2 (MRI)	*D6 (PA)*	*C/O/U*
1	T0	CIS	U
2	Ta–1	pTa	˜C
3	Ta–1	pTa	˜C
4	T2	pTa	O
5	Ta–1	pTa	˜C
6	T3b	pT3b	C
7	T3a	pT3a	C
8	T3a	pT2	˜C
9	Ta–1	pT1	˜C
10	T0	pTa	U
11	Ta	pTa	C
12	T3b	pT3b	C
13	Ta	pTa	C
14	Ta–1	pTa	˜C
15	T4a	pT4a	C

[1] C: Correct staging
˜C: Almost correct staging, difference is without therapeutic consequences
O: Overstaging
U: Understaging

cinoma could be diagnosed correctly in 9 of 10 cases (Fig. 2). The case of incorrect staging was due to superficial tumour calcification.

In Table 3 the results of MRI staging are compared with the final diagnosis. In the group with invasive bladder carcinoma ($\geqslant$pT2), MRI was correct in all cases (Fig. 3). For superficial bladder carcinoma ($<$pT2), MRI has its limitations. One small tumour (3 mm) and the tumour in the patient with carcinoma *in situ* could not be diagnosed. One pTa tumour was overstaged as pT2.

In Table 4 the staging results of D2 (MRI) and D5 (US) were combined. There was only 1 case of overstaging in the group of superficial tumours by ultrasound, due to the superficial calcification of the tumour mentioned earlier. However, double-surface coil MRI correctly staged this tumour. Both

Table 4 Comparison of MRI, US and Pathological Stage

	D2 (MRI)	*D5 (US)*	*D6 (PA)*	
1	U	˜C	CIS	
2	˜C	˜C	pTa	
3	˜C	˜C	pTa	
4	O	˜C	pTa	
5	˜C	˜C	pTa	
6	C	U	pT3b	
7	C	O	pT3a	
8	˜C	˜C	pT2	
9	˜C	O	pT1	← calcification
10	U	˜C	pTa	
11	C	˜C	pTa	
12	C	U	pT3b	
13	C	˜C	pTa	
14	˜C	˜C	pTa	
15	C	˜C	pT4a	

[1] C: Correct staging
˜C: Almost correct staging, difference is without therapeutic consequences
O: Overstaging
U: Understaging

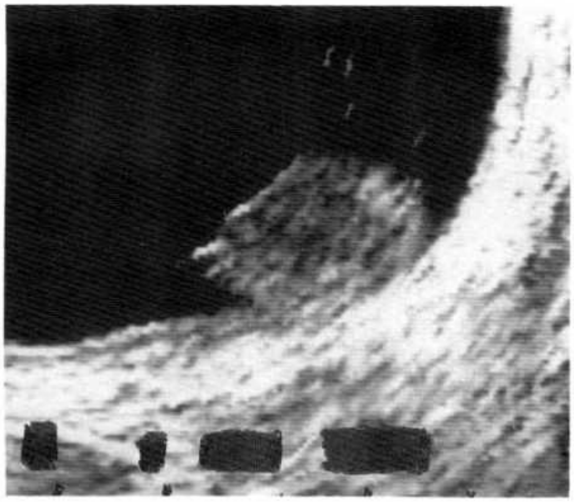

Fig. 2 Case 3. Intravesical ultrasound (5.5 MHz) showing tumour on the left bladder wall. Infiltration into the bladder wall cannot be established. The mucosa on the right side of the tumour is clearly visible (due to oedema). (2 cm per division).

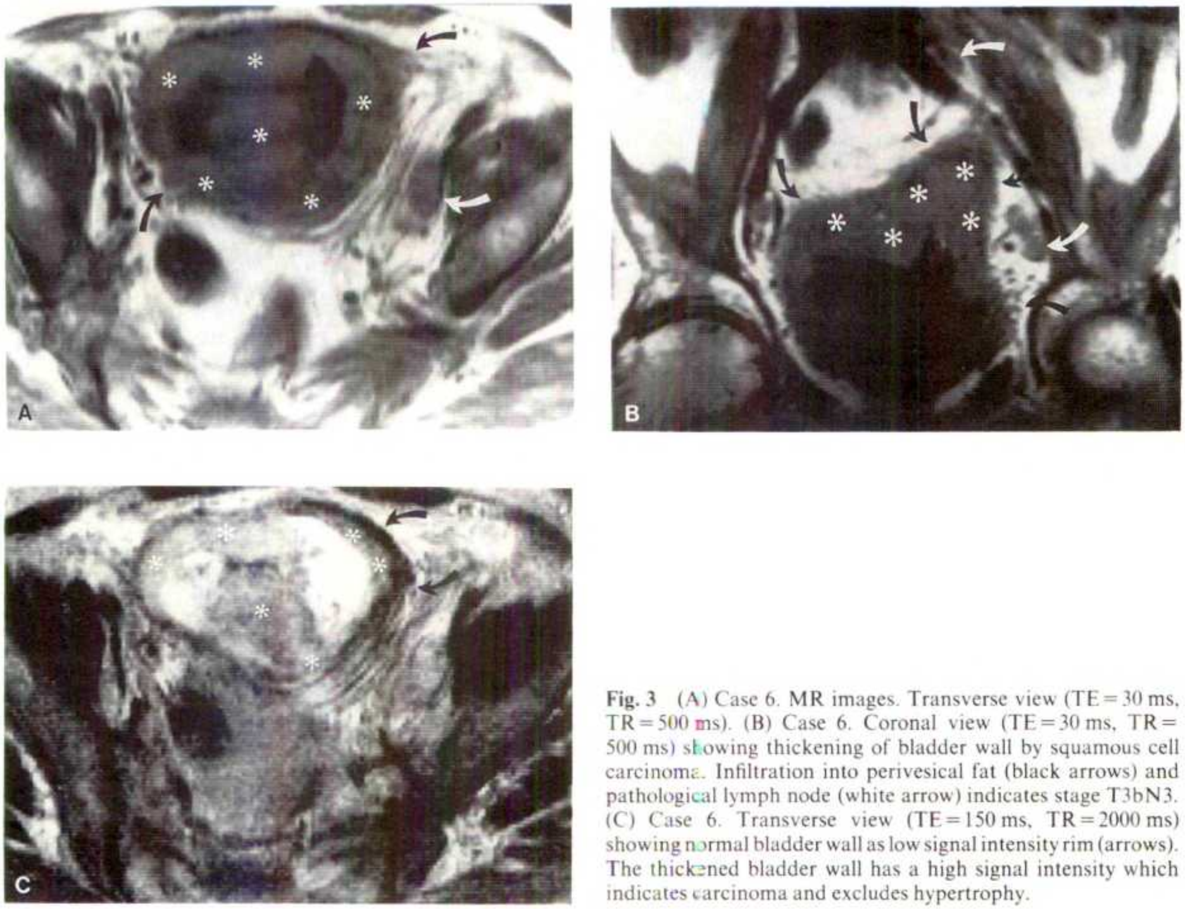

Fig. 3 (A) Case 6. MR images. Transverse view (TE = 30 ms, TR = 500 ms). (B) Case 6. Coronal view (TE = 30 ms, TR = 500 ms) showing thickening of bladder wall by squamous cell carcinoma. Infiltration into perivesical fat (black arrows) and pathological lymph node (white arrow) indicates stage T3bN3. (C) Case 6. Transverse view (TE = 150 ms, TR = 2000 ms) showing normal bladder wall as low signal intensity rim (arrows). The thickened bladder wall has a high signal intensity which indicates carcinoma and excludes hypertrophy.

methods are complementary; neither over- nor under-staging occurred when using both techniques (Table 4).

Table 5 shows that the conventional screening method without anaesthesia (D1) led to 3 cases of understaging. Bimanual examination under anaesthesia (D4) produced a better result in only 1 of those 3 cases.

CT (performed in only 5 patients) produced 3 cases of correct tumour staging and 2 of understaging.

For staging of the lymph nodes, CT was correct in 3 cases and the tumour was understaged in 2. For those 5 cases, MRI produced 2 correct staging results but also 3 instances of understaging, probably due to suboptimal sequences (Table 6).

Discussion

Although clinical staging of bladder tumours according to the UICC "minimal requirements" is still used in daily urological practice, the overall results are not satisfactory (Table 7). From our results we found 2 cases of under- and 1 of over-staging, even under anaesthesia. New diagnostic techniques such as MRI and US have their own characteristics (Fisher *et al.*, 1985). The improvement in staging of penetrating bladder tumours is mainly due to the MRI using a double-surface coil. This surface coil gives a better signal to noise ratio (SNR), as described by Barentz *et al.* (1988). Therefore, the delineation of the bladder wall, the visualisation of the tumour itself and the tumour invasion at all levels are better in patients with penetrating tumours (Tables 3 and 4). The disadvantages of MRI are the high cost of the investigation, the immobilisation of the patient and a relatively long investigation time. On the other hand, MRI can be performed on an out-patient basis, no radiation is involved, no contrast medium is needed and no artefacts are seen (Bryan *et al.*, 1983; Hricak and Williams, 1984).

Ultrasonography is a reliable method for staging superficial bladder cancer (Nakamura and Niijima,

Table 5 Comparison of D1, D4 and D6

	D1		*D4*		*D6 (PA)*
1	CIS	C	CIS	C	CIS
2	Ta–1	~C	Ta–1	~C	pTa
3	Ta–1	~C	Ta–1	~C	pTa
4	Ta–1	~C	Ta–1	~C	pTa
5	Ta–1	~C	Ta–1	~C	pTa
6	T2	U	T3a	U	pT3b
7	Ta–1	U	T2	~C	pT3a
8	T2	C	T3b	O	pT2
9	Ta–1	~C	Ta–1	~C	pT1
10	Ta–1	~C	Ta–1	~C	pTa
11	Ta–1	~C	Ta–1	~C	pTa
12	T3b	C	T4	~C	pT3b
13	Ta–1	~C	Ta–1	~C	pTa
14	Ta–1	~C	Ta–1	~C	pTa
15	T3a	U	T3a	U	pT4a (Wolffian duct tumour)

[1] C: Correct staging
~C: Almost correct staging, difference is without therapeutic consequences
O: Overstaging
U. Understaging

Table 6 Comparison of Final Pathological Result, MRI and CT in Tumour and Lymph Node Staging

	D2 (MRI)		*D3 (CT)*		*D6 (PA)*
1	sN0				
2	sN0				
3	sN0				
4	sN0				
5	sN0				
6	T3bN0	C C	T3aN0	U C	pT3b N0
7	T3aN0	C U	T3aN1	C C	pT3a N1
8	T3aN0	~C U	T3aN0	~C U	pT2 N4
9	sN0				
10	sN0				
11	sN0				
12	T3bN0	C U	T3bN2	C U	pT3b N4
13	sN0				
14	sN0				
15	T4aN0	C C	T0N0	U C	pT4a N0

s = Superficial
[1] C: Correct staging
~C: Almost correct staging, difference is without therapeutic consequences
U · Understaging

1980). The limitations of the technique do not permit differentiation between Ta, T1 and CIS (Denis *et al.*, 1984). In deeper layers, artefacts are often seen and beyond the level of T2 further differentiation is difficult (Gammelgaard and Holm, 1980; Denis *et al.*, 1984; Jaeger *et al.*, 1984; Schmidbauer *et al.*, 1984). Intravesical ultrasonography is an invasive procedure but it can be performed under anaesthesia after cystoscopy and before transurethral resection. It is a relatively inexpensive technique which is easy to repeat and simple to learn. Although Denkhaus *et al.* (1985) successfully screened bladder tumours by transabdominal ultrasound, they concluded that the intravesical approach gave more accurate results. Gammelgaard and Holm (1980) and Jaeger *et al.* (1985) compared the transrectal with the transurethral route and concluded that the transurethral approach gives the most reliable results. We used the endovesical method. Overstaging can be partly due to calcification on the tumour surface, which will obstruct ultrasonic propagation (Gammelgaard and Holm, 1980; Jaeger *et al.*, 1984). Other errors of over- and under-staging are due to small tumour size and the presence of scar tissue. If the tumour is larger than 3 cm, a tendency towards overstaging is likely (Jaeger *et al.*, 1986). According to Denkhaus *et al.* (1985), this is due to the loss of penetration and the short focusing of the transducer used. Errors in staging can also be produced by blood clots, chronic cystitis or trabeculation of the bladder, diagnosed as a tumour (pTa–1–is) (Gammelgaard and Holm, 1980; Jaeger *et al.*, 1984).

MRI is, however, capable of differentiating blood clots and trabeculation from cystitis and carcinoma (Fisher *et al.*, 1985; Barentz *et al.*, 1988).

Jaeger *et al.* (1986) mentioned only a small improvement of 3% in tumour staging by ultrasonography compared with the conventional method.

At least one advantage of intravesical ultrasonography is the possibility of diagnosing a bladder tumour in a diverticulum, which by UCS could not be seen (Walther and Schüller, 1983).

Abu-Yousef *et al.* (1984) reported that the accuracy of CT in bladder staging is low, especially in lower stage tumours (pTa–3a), and that penetration in the bladder dome and the prostate is not adequately demonstrated by CT. Estimates of the overall accuracy of CT staging of bladder tumours vary widely, with rates ranging from 59 to 88% (Arger, 1985). One of the problems in staging bladder tumours by CT is the near-identical density of normal and abnormal tissue in solid tumours, whereas MRI is capable of distinguishing between tumour and bladder wall and also between tumour and perivesicular fat (Denis *et al.*, 1984; Barentz *et al.*, 1988). Other deterrent factors are artefacts due to previous transurethral resection, partial cystectomy or radiation.

Lymph node involvement is of great importance and because the 7 to 10% morbidity rate of regional lymph node dissection, an accurate non-invasive

Table 7 Bladder Tumour Staging according to the Minimal Requirements of UICC: Comparison of Pre-treatment and histopathological T category

	pTA/pT1			*pT2–4*			
	n	*Ac (%)*	*Ov (%)*	*n*	*Ac (%)*	*Un (%)*	*Ov (%)*
Bartels *et al.* [33], 1983	25	100	—	21	76	24	—
Lang [8], 1969	12	100	—	18	50	50	12
Marshall [9], 1952 (no biopsies)	25	21	79	86	59	30	12
Murphy [10], 1978	18	67	33	58	47	48	5
Richie *et al.* [4], 1975	49	78	22	45	36	62	2
Skinner [5], 1977	nd	nd	nd	nd	37	42	21
Vakarakis *et al.* [6], 1975	18	78	22	48	25	73	2
Wajsman *et al.* [11], 1975	26	46	53	32	38	31	31
Whitmore *et al.* [7], 1977	22	100	—	81	68	25	7

T categories: TA/T1, T2, T3a, T3b, T4. Ac = Pre-treatment T category correct; Un = understaging; Ov = overstaging; nd = no data

method would be extremely helpful (Arger, 1985). Lymph node involvement detected by CT ranged from 73 to 88% (Arger, 1985). Engelmann *et al.* (1984) reported an accuracy rate of 99%. If the lymph node enlargement is less than 1.5 cm, CT will often give a false-negative result. Our series is too limited to be able to discuss which technique is better for the detection of lymph node involvement.

Problems in the staging of bladder tumours are particularly related to the assessment of the depth of invasion and the involvement of lymph nodes. Conventional staging methods described by Jewett and Strong (1946) and Marshall (1952) and propagated by the UICC (1978) are not accurate. Although our series is small, it is concluded that intravesical ultrasonography is reliable for the differentiation between superficial (pTa-1-is) and penetrating ($\geqslant$pT2) bladder tumours. CT, especially double-surface coil MRI, is satisfactory in defining the depth of tumour penetration in infiltrating tumours. More extensive testing is needed to show if the combination of ultrasound and MRI will achieve greater accuracy in the pre-operative staging of bladder tumours.

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Adjuvant Laser Treatment of Bladder Cancer: 8 Years' Experience with the Nd-YAG Laser 1064 nm

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Summary—Following the development of suitable equipment for the endoscopic application of an Nd-YAG laser in this department, the laser has been used routinely in the management of bladder cancer since 1978. To evaluate side effects and efficiency, 252 consecutive laser treatments were evaluated with a minimum follow-up of 12 months. Side effects were few (0.3% perforation) and patients tolerated the treatment very well. The general recurrence rate of T1 tumours varied from 33% for primary carcinomas to 54% for recurrent tumours, but the incidence of local recurrence was only 7%. The long-term results of laser treatment showed a decrease in the local recurrence rate when compared with the results of conservative electocautery resection, but there was no significant influence on the total recurrence rate.

Endoscopic Nd-YAG laser irradiation has been established as an alternative form of treatment for bladder cancer. The indications have been extended to include treatment of urethral strictures (Smith and Dixon, 1984), cancer of the prostate (Beisland and Sander, 1986) and tumours of the upper urinary tract (Hutschenreiter *et al.*, 1986). A wave length of 1064 nm (Nd-YAG) produces a predictable deep coagulative necrosis whilst maintaining the structural integrity of the irradiated tissue (Keiditsch, 1981). This should improve the management of transitional cell cancer of the bladder. We present the clinical results and side effects of 252 endoscopic laser procedures carried out in the treatment of bladder cancer since 1978.

Patients and Methods

Between November 1978 and May 1986, 402 endoscopic laser treatments of transitional cell cancer of the bladder have been performed. The male to female ratio was 3 to 1 and the patients' ages ranged from 48 to 89 years. This is similar to the normal distribution of sex and age seen in patients with bladder cancer. All those reviewed were graded histologically. The staging of patients with large tumour masses or evidence of muscle invasion was performed by CT scans and intravesical sonography. NMR scans have also been performed since 1983.

The follow-up protocol consisted of cystoscopy and exfoliative cytology carried out at 3-monthly intervals The minimal follow-up was 12 months. All patients with incomplete follow-up or insufficient documentation were excluded. Thus the number of treatments reviewed was reduced to 252. The drop-out rate was 32 to 43% in all groups due to incomplete follow-up.

Laser energy (1064 nm) was delivered by a Medilas model MBB and transmitted by quartz fibres (0.6 mm) into the tissue by means of specially designed cystoscopic inserts (Fa. Storz) directed with an Albarran lever. By this means, even the region of the bladder outlet was accessible to irradiation. The outlet divergence of the fib was 10° decrease, with a power loss of 10% in cases of maximal flexion. To prevent possible retinal damage protective filters were worn during cystoscopy.

The operation was usually performed under spinal anaesthesia but in high risk patients (n = 8) local anaesthesia was used. Muscle relaxation was not necessary for laser therapy. Laser coagulation of the tumour base was performed to seal the lymphatics and to prevent the spread of tumour

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cells. In tumours < 0.5 cm diameter, and in patients with evidence of infiltration, a pre-operative staging, transurethral resection was also performed. In smaller tumours, tissue for histological examination was first removed using biopsy forceps. The selected area of bladder wall was usually obtained by filling the bladder with 200 ml physiological saline.

Adhering clots were removed before laser treatment in order to avoid a serious loss of laser light penetration induced by the higher absorption of haemoglobin. A power output of 40 to 50 watts was selected and continuous wave energy applied to a given area for 3 to 4 s. Tumours and the surrounding area (= 2 mm) were irradiated uniformly by moving the instrument up and down. In most cases blanched necrosis of the tissue provided optical control of the effectiveness of therapy, but with extensive tumours the shaggy, irregular appearance of the crater meant that the visible changes were unreliable in determining the adequacy of treatment. Foley catheter drainage was maintained post-operatively for 1 to 2 days.

Results

The value of laser therapy varied with the stage and grade of the tumours. The general recurrence rate of primary tumours ranged from 33% in stage A to 55% in stage B (Table 1). Recurrent tumours (1–5 recurrences) had an even worse prognosis. In these comparable groups the recurrence rate ranged from 54% in stage A to 75% in stage B. Primary tumours, as well as recurrent tumours of higher stage and grade, had a higher rate of recurrence. There was no significant difference in the disease-free intervals, which ranged from 9 to 16 months (Table 2).

There were fewer local recurrences (Table 3). The mean local recurrence rate was only 7%, with no significant difference between primary and recurrent tumours, including only potential curative treatments of stage A and B tumours. Nd-YAG laser treatment of the bladder is a simple and safe technical procedure for both staff and patients. The one severe complication we saw was an injury of the small bowel, due to a technical failure of power control, which presented with signs of local peritonitis on day 3. All other side effects, such as cystitis, seemed to be induced by transurethral manipulation and were not specifically due to the laser therapy (Table 4).

Table 1 Recurrence Rates after Laser Treatment of Primary Bladder Carcinomas in Correlation to Staging

Stage/grade	*No of patients*	*No. of recurrences*	*Per cent recurrence*	*Mean interval (months)*
A G1/G2	42	14	33	10
A G3/G4	6	4	66	15
B G1/G2	25	14	55	16
B G3/G4	13	12	92	13
C G1/G4	6	5	83	9

Table 2 Recurrence Rates after Laser Treatment of Recurrent Tumours Correlated with Staging and Grading of Bladder Tumours

Stage/grade	*No of patients*	*No. of recurrences*	*Per cent recurrence*	*Mean interval (months)*
A G1/G2	86	47	54	9
A G3/G4	10	7	70	11
B G1/G2	41	31	75	10
B G3/G4	17	14	82	12
C G1/G4	6	6	100	9

Table 3 Local and Distant Recurrence of Tumours Following Laser Therapy of Bladder (G1/G2)

	Local recurrence (%)	*Non-local recurrence (%)*
Primary tumour (n = 77)	5	35
Recurrent tumour (n = 127)	8	53
Total	7	46

Table 4 Complications after Combined ND-YAG Laser Treatment of Bladder Cancer

Complications	*No*	*%*
Perforation (bowel)	1	0 4
Haemorrhage	0	0
Mild cystitis	13	5
Severe cystitis	10	4
Urethral stenosis	15	6

Discussion

The effect of lasers on tissue depends both on wavelength and on irradiation modality. Continuous wave irradiation of 1064 nm (Nd-YAG laser) produces a deep coagulative necrosis of 3 to 5 mm, using a power of 40 watts and an irradiation time of 3 s (Keiditsch, 1981; Staehler *et al.*, 1981). The bladder wall maintains its structural integrity and heals by secondary collagen deposition (Pensel, 1986). Complete healing is achieved after 4 to 6 weeks.

These effects have formed the basis for using the Nd-YAG laser in the treatment of bladder cancer. Our results with non-invasive tumours showed good local control with few side effects.

Despite their initial expectations and the clinical results reported by Hofstetter and Frank (1983) and Staehler *et al.* (1985), analysis of 252 laser treatments showed no significant reduction in the general recurrence rate when compared with the results of transurethral electrocautery resection. We found a similar trend in our prospective randomised study and this was confirmed by Beisland and Seland (1986) in a comparative study of 112 patients. However, our low local recurrence rate (7%) suggests that laser therapy has a significant influence on this rate, which was 25% after conventional electrocautery resection (National Bladder Cancer Collaborative Group A, 1977). A similar decrease was noted by Beisland and Seland (1986).

Severe problems arise in the treatment of muscle-invading tumours. Theoretically, such tumours of the bladder can be irradiated effectively by transurethral laser treatment. However, pre-operative staging, even with CT and NMR scans (Beer *et al.*, 1985; Amendola *et al.*, 1986), does not give a sufficiently accurate assessment of muscle invasiveness and can lead to significant errors in clinically understaging bladder cancer (Smith *et al.*, 1982). As a result, a "treatment failure" in understaged patients might be deduced. Our poor results in higher stage tumours are similar to those of Smith and Dixon (1984) and might be explained in this way.

We know from experimental data (Keiditsch, 1981; Staehler *et al.*, 1981) that the vertical penetration of laser light is limited and to optimise this vertical coagulation it is necessary to combine the therapy with previous electrocautery resection. When treatments are combined, however, it is difficult to assess their individual efficiency, results and side effects. We therefore recommend circular laser coagulation of tissue at the tumour base before electro-resection, thereby sealing the lymphatics and inducing vascular stasis.

The use of the Nd-YAG laser in the treatment of cancer of the bladder improves treatment significantly and, in combination with electro-resection, reduces local recurrences and minimises surgical complications in the management of larger tumours. Small tumours (<0.5 cm) can be treated effectively by laser therapy alone, under local anaesthesia, and without the need for catheter drainage and hospitalisation.

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Linitis Plastica-like Carcinoma of the Urinary Bladder

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Summary—Two cases of signet-ring cell adenocarcinoma of the urinary bladder with a linitis plastica pattern of infiltration were studied. Mucin histochemistry indicated the presence of neutral and acid mucopolysaccharides and absence of sulphomucin. Immunocytochemistry of the tumour cells was positive for keratin and carcinoembryonic antigen, but negative for prostatic specific antigen and vimentin. The relevance of these observations to the differentiation and histogenesis of these tumours is discussed.

Adenocarcinoma of the urinary bladder is rare, comprising approximately 2% of all epithelial malignancies of the bladder. Adenocarcinomas of the bladder consisting purely, or chiefly, of signet-ring cells are even more uncommon, although admixture of signet-ring cells with other adenocarcinomatous patterns is not as infrequent (Johnson *et al.*, 1985). The few cases of this neoplasm that are reported in the literature illustrate a typically diffuse infiltrative pattern similar to linitis plastica of the stomach (Mostofi *et al.*, 1955; Saphir, 1955; Braun *et al.*, 1981; Kondo *et al.*, 1981; Yoshida *et al.*, 1981; Choi *et al.*, 1984; Kumar *et al.*, 1986).

We have studied two patients using immunocytochemical and mucin histochemical techniques to define some of the phenotypic expressions of these neoplasms and their histogenesis.

Patients and Methods

Two cases of primary signet-ring cell carcinoma of the urinary bladder were studied. Formalin fixed and paraffin embedded sections were stained with H and E, periodic acid Schiff with and without diastase, combined periodic acid Schiff and Alcian blue, pH 2.5 (PAS/AB), combined high iron diamine and Alcian blue, pH 2.5 (HID/AB), and mucicarmine. Immunocytochemical studies were performed using the avidin biotin complex (ABC) method (Hsu *et al.*, 1981).

The following antibodies were used:

(a) Monoclonal antibodies to cytokeratin AE1–AE3, dilution 1/100 (Hybritech, La Jolla, CA-USA).

(b) Monoclonal antibody to Vimentin, dilution 1/100 (Biogenex, Dublin, CA-USA).

(c) Polyclonal antibodies to carcinoembryonic antigen (CEA), dilution 1/800.

(d) Polyclonal antibodies to prostate specific antigen (PSA), dilution 1/200, both (c and d) obtained from DAKO, Santa Barbara, CA-USA.

Case Reports

Case 1. A.M.S.M., a 46-year-old Filipino male, was first seen as an out-patient at Hamad General Hospital in August 1986 with a 1-month history of terminal haematuria, increased frequency and strangury. He had passed 2 small stones *per urethram* 1 week earlier. He remembered having had mild haematuria several months earlier, which cleared spontaneously. Physical examination revealed no abnormality. The urinary bladder was not distended. The prostate was of normal size on rectal examination. Urinary flow studies showed normal values. Urine analysis revealed more than 100 RBCs per high power field. Urine culture was negative. Various blood chemistry and haematological examinations were all within normal limits.

An intravenous urogram showed normal upper tracts. The bladder showed irregularity of the anterior wall and a large post-voiding residue. Cytology of the urine revealed the presence of signet-ring cells with hyperchromatic nuclei. A CT scan showed a large tumour involving the anterior wall and dome of the bladder.

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There was no evidence of involvement of lymph nodes or adjacent organs. The barium meal follow-through, barium enema studies and chest X-ray were normal.

At cystoscopy, a large growth with necrotic areas was seen occupying the anterior wall and dome of the bladder. The rest of the bladder (apart from trabeculation) and the urethra appeared normal. Bimanual examination under anaesthesia showed the bladder to be mobile. Biopsy confirmed a signet-ring cell carcinoma.

In October 1986 a total cystectomy and an ileal conduit were carried out. No enlarged lymph nodes were found. He was discharged home in November 1986. He returned to the Philippines and died approximately 10 months after the initial diagnosis. Further information could not be obtained.

Case 2. A 51-year-old Qatari man was seen at Hamad General Hospital in November 1986 with 1-year history of recurrent haematuria associated with increasing frequency and strangury. He had been involved in a road traffic accident a year earlier, which resulted in fracture of the left forearm bones. There was no organomagaly. Rectal examination revealed a normal prostate.

Intravenous urography showed irregularity of the dome of the bladder. The upper tracts were normal and there was no post-micturition residue. A CT scan revealed involvement of the anterior and left lateral bladder wall by a tumour with extravesicular, anterior extension. No lymph nodes or involvement of the adjacent organs were detected. The chest X-ray was normal.

At cystoscopy, the presence of a tumour at the above site was confirmed. Bimanual examination showed diffuse thickening of the anterior wall of the bladder. A transurethral biopsy showed a signet-ring cell adenocarcinoma. A subtotal cystectomy was performed in another country in December 1986. He was seen again in Qatar in September 1987, when cystoscopy and biopsy showed no recurrence.

Results

Gross pathology

In Case 1, the cystectomy specimen consisted of the entire urinary bladder, prostate and seminal vesicles. The bladder (Fig. 1) was diffusely infiltrated, especially at the dome extending into the proximal two-thirds of the bladder in all directions. The epithelial surface was oedematous and focally ulcerated. The cut surface had a greyish white, gelatinous, linitis plastica appearance involving full wall thickness and penetrating to perivesicular fat at the peak of the dome. The lower third of the bladder, urethra, prostate and seminal vesicles were grossly free from tumour. In case 2, the subtotal cystectomy specimen was not available for examination but CT scan and cystoscopic examinations suggested a linitis plastica appearance with anterior extension to perivesicular fat.

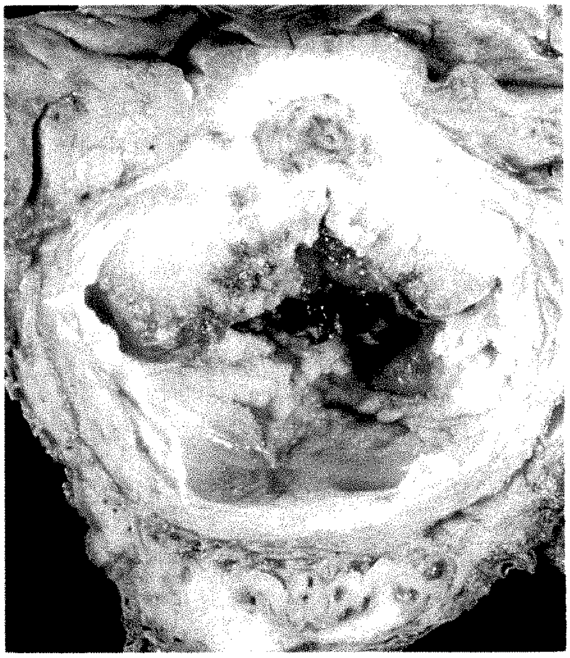

Fig. 1 Total cystectomy specimen (Case 1) showing diffuse linitis plastica infiltration of the wall with extension to perivesicular tissue proximally.

Light microscopy

The adenocarcinoma in Case 1 was composed purely of signet-ring cells (Fig. 2) infiltrating the full wall thickness into perivesicular fat. Lakes of mucin were present in a few foci. The prostate and seminal vesicles were free. The bladder urothelium over the tumour, or in uninvolved parts, was of transitional cell type with no evidence of metaplastic changes. No cystitis glandularis was noted in multiple sections examined. Exceptionally, a single benign cell in the urothelium contained a minute Alcian blue positive droplet in the cytoplasm. The microscopic apperances in Case 2 were essentially the same. The tumour cells occasionally formed minute tubular aggregates. Foci of cystitis glandularis were present, as evidenced by a few benign crypts lined by tall cells displaying minute and elongated basal nuclei and finely vacuolated clear cytoplasm.

Mucin histochemistry and immunocytochemistry

Mucin stains indicated the presence of neutral and acid mucopolysaccharides.

There was positive cytoplasmic staining with

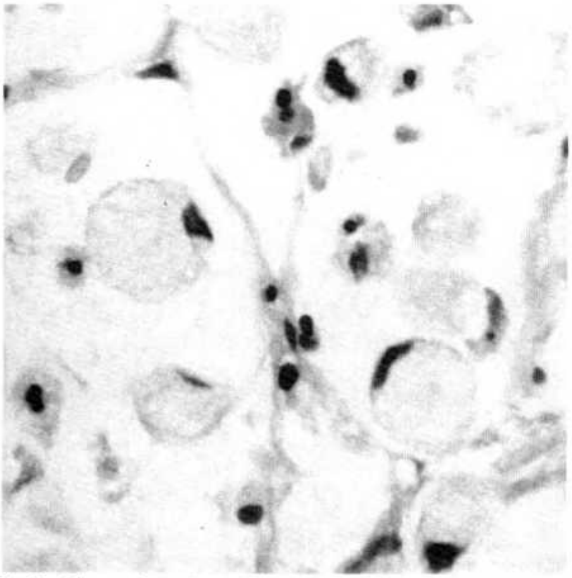

Fig. 2 Signet-ring cells infiltrating urinary bladder wall. (H and E ×290).

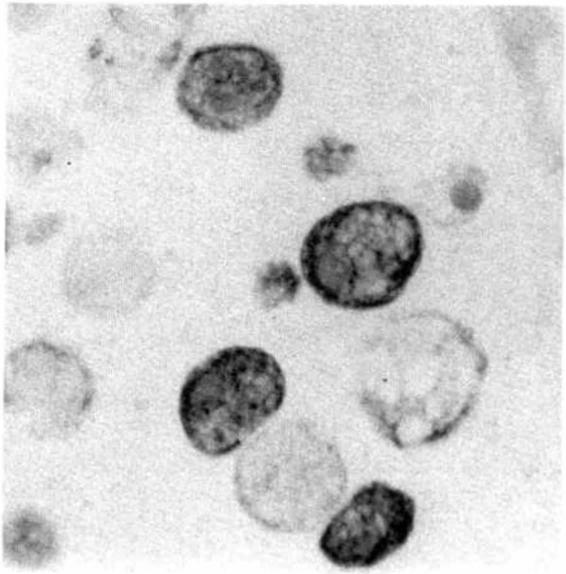

Fig. 3 Positive cytoplasmic keratin immunostaining of the signet-ring cells. (ABC peroxidase ×290).

PAS following diastase treatment, with mucicarmine and with Alcian blue. Staining with HID was negative, indicating the absence of sulphomucins. Tumour cells in both cases showed positive cytoplasmic staining for keratin (Fig. 3) and CEA (Fig. 4). There was no staining of tumour cells for vimentin or prostatic specific antigen.

Discussion

Linitis plastica is a descriptive term first coined by William Brinton for an inflammatory condition of the stomach in the book entitled "Diseases of the Stomach", published in 1859 (Ming, 1973). This term has subsequently been widely applied to a diffuse carcinoma of the stomach. Linitis plastica carcinomas have also been described in other sites including the colon, small intestine, gall bladder, appendix and, most recently, the oesophagus (Chejfec *et al.*, 1983).

In the urinary bladder, most cases of signet-ring carcinomas show a diffuse linitis plastica-like infiltration of the bladder wall; very few may show discrete masses in association with diffuse infiltration. Histologically, various other morphological patterns have been seen in association with signet-ring cells. They include irregular glandular structures, foci of transitional cell carcinoma and, in very rare instances, areas of squamous cell differentiation (Choi *et al.*, 1984).

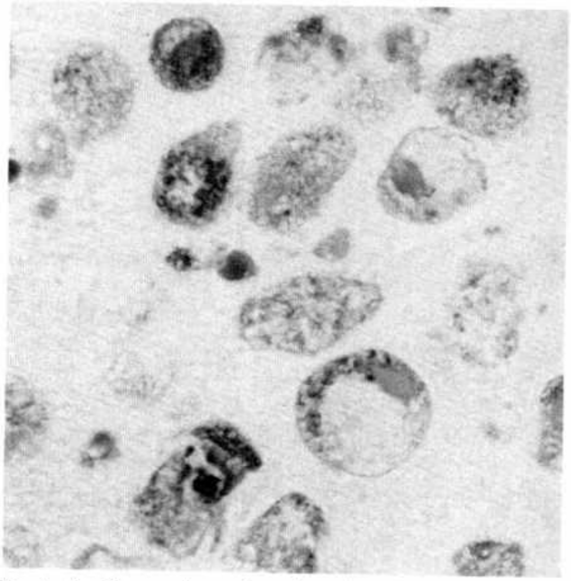

Fig. 4 Positive carcinoembryonic antigen immunostaining of the signet-ring cells. (ABC peroxidase ×290).

The immunocytochemical findings in our cases are consistent with a malignant epithelial tumour (positive keratin, positive CEA). There is no evidence of prostatic origin (negative PSA). This is comparable with a negative immunoperoxidase staining for prostatic acid phosphatase performed in a previous case showing that the vacuoles and cytoplasm of the signet-ring cells are negative for acid phosphatase (Gonzalez *et al.*, 1982). Coexpression of intermediate filaments is not present, as seen in some carcinomas (negative vimentin). The mucin histochemistry pattern corresponds to a small bowel differentiation; there is no evidence of the presence of sulphomucins because HID is negative. Sulphomucins are normally present in the colon and their presence is detected by HID or Alcian blue pH1.

The origin of the mucinous adenocarcinomas of the urinary bladder has been attributed to remnants of the cloaca or the totipotential transitional cell epithelium of the bladder. In our opinion, signet-ring cells are a function of cell differentiation rather than histogenesis (Gould, 1986). The concepts applied to the gastrointestinal tract can be extended to explain this variant of adenocarcinoma of the urinary bladder. In the bowel, stem cells differentiate into all 4 types of intestinal mucosal cells; similarly, stem cells in the stomach are capable of differentiating into the various types of gastric mucosal cells, including parietal cells. The concept of differentiation implies the ability of primitive cells, subject to different stimuli, to develop various morphological types, from tall cylindrical cells to mucin-rich signet-ring types.

The prognosis of linitis plastica carcinoma of the urinary bladder is poor. Although the number of patients is small, 60% died within 15 months from the time of diagnosis. Longer survival was seen in patients who underwent radical cystectomy. Metastatic sites included lymph nodes, bone, pericardium, meninges, ovaries and pleura. The preferred treatment was radical cystectomy because the tumour was resistant to radiation therapy or chemotherapy (Choi *et al.*, 1984).

Our first patient died 8 months after radical cystectomy. The second patient was well and alive 16 months following the initial diagnosis.

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The Risk of Radical Cystectomy

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Summary—A review of the operative risk of cystectomy and urinary diversion performed by one surgeon at one institution over an 8½-year period was performed. Operative mortality was 0.4% (1/229). There were no urinary leaks, 1 bowel leak, 2 bowel obstructions, no rectal injuries and 3 pelvic abscesses. Cystectomy is a safer operation than is usually appreciated, based on improvements in pre-operative preparation, intra-operative monitoring and blood product replacement, and post-operative support if a complication does occur.

Radical cystectomy with urinary diversion has traditionally been regarded as one of the most difficult urological procedures (Whitmore, 1975). The length of the operation, the multiple steps needed during the procedure, and the age and general health of the patients heighten the potential for a complication. Over the last 30 years, the operative mortality rate has decreased from 10–20% to 1–3% (Whitmore, 1975; Skinner *et al.*, 1982, 1987; Smith *et al.*, 1982). Improvements in pre-operative preparation of the patient, intra-operative anaesthesia monitoring, blood product replacement and support of the patient if a post-operative complication does develop have all contributed to the increasing safety of the operation. This report presents our experience with the procedure.

Patients and Methods

All cystectomies performed between August 1979 and January 1988 by one surgeon (J.E.M.) at one institution were reviewed. No exclusions were made. Patients who had had previous definitive radiation therapy (21 patients), various forms of pre-operative radiation therapy ranging from 20 Gy photon irradiation (19) to 50 Gy mixed beam (combined photon and neutrons) (6), alternative forms of urinary diversion (*e.g.* continent ileal or caecal cutaneous reservoir (15) or ileal or caecal reservoir to the urethra (13)) and pre-operative systemic chemotherapy (19) were included. Pre-operative radiation therapy has not been used since 1984.

Hospital mortality was defined as any death in the hospital after the operation or <30 days after the operation. Acute technical complications of a serious nature were tabulated. Late complications (>30 days after discharge) were not included.

Results

Between August 1979 and January 1988, 229 cystectomies and urinary diversions in a single stage were done, primarily for bladder cancer. Approximately 85% of the patients had an ileal conduit diversion. Their ages ranged from 38 to 87 years.

The operative mortality rate was 1/229 (0.4%). Other complications are listed in the Table. Routine peri-operative total parenteral nutrition (TPN),

Table Technical Complications

Type	*No. (%)*
Urine leak	0 (0)
Bowel leak	1 (0.4)
Bowel obstruction requiring reoperation	2 (0.8)
Wound dehiscence	1 (0.4)
Acute obstruction requiring percutaneous nephrostomy	2 (0.8)
Pelvic haematoma requiring reoperation	1 (0.4)
Pelvic abscess	3 (1)
Death	1 (0.4)

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digitalis, anticoagulation or intensive care monitoring were not used.

The one operative death occurred after a combined salvage cystectomy, left nephroureterectomy and urethrectomy in a 77-year-old man with mucosal transitional cell carcinoma from the renal pelvis to the distal urethra. He had angiographically documented inoperable coronary artery disease and surgery was necessary because of intractable haematuria and lower tract symptoms. He died of a myocardial infarction 10 days post-operatively.

Discussion

The purpose of this review is to emphasise that radical cystectomy in the 1980s is a much safer operation than is commonly realised. One cannot minimise the severity of the procedure because great stress is placed on the patient. However, cystectomy appears to be the most effective method for the treatment of high stage bladder cancer; integrated radiation therapy and/or chemotherapy with or without surgery may provide better results, but it will probably be several years before firm conclusions can be drawn.

Improvements in patient rehabilitation with the use of a penile prosthesis or intracorporeal injection of vasoactive drugs for post-operative impotence, together with forms of urinary diversion that either avoid an external stomal appliance or avoid a stoma completely, make the operation more acceptable to the patient. A recovery period of 4 to 6 weeks is still needed before the patient feels well but the lower morbidity of the operation is noteworthy. Many factors have contributed to the decreasing risk of cystectomy.

Pre-operative factors

Nutrition. The pre-operative nutritional status of the patient is an important variable relative to the risk of post-operative complications. Earlier studies at this institution suggested that 80 to 90% of patients undergoing a cystectomy were either normal or only slightly nutritionally depleted prior to surgery and the complication rate in these patients was low. Approximately 10% had moderate to severe depletion and might have benefited from peri-operative nutritional support. We felt that administering TPN or tube feeding to all patients was unlikely to lower the complication rate significantly and might expose them to other risks. We do consider pre-operative nutritional support in patients who have had a marked weight loss or who have hypoalbuminaemia; in such cases a formal nutritional assessment is performed. In other situations, nutritional support is added only if the return to normal bowel function is delayed or if another complication occurs which would justify nutritional support. Approximately 5 to 10% of patients will need post-operative nutritional support. Routine peri-operative improved nutrition might lessen the weight loss which accompanies the operation and might hasten the return to normal activity, but this has not been proved beyond doubt. We think it unlikely that routine peri-operative nutrition has a significant impact on the length of hospital stay in spite of data suggesting the contrary (Askanazi *et al.*, 1986).

Cardiovascular status. Patients with significant cardiovascular or pulmonary disease require special attention. They are often heavy smokers and bronchodilators, antibiotics and aggressive respiratory therapy are often helpful. A history of significant cardiac disease indicates the need for further measures. Pre-operative testing for cardiac reserve either with stress testing or coronary angiography may be appropriate. In patients with marginal cardiac reserve, the pre-operative placement of a Swan-Ganz monitoring catheter helps to provide optimal volume status and to judge the cardiac response to volume shifts. This allows the anaesthetist to have an index of the patient's tolerance to fluid challenges and depletions.

Bowel preparation. In recent years we have used a 1-day bowel preparation with either a 10% mannitol solution or a Go-lytley solution. Clear liquids only are given on the day before surgery. Systemic antibiotic coverage is used with a cephalosporin by itself or in combination with an anaerobic coverage such as metronidazole. Oral antibiotics were used only in the earlier years of this study. Wound infections or pelvic abscesses are now extremely uncommon.

Intra-operative procedures

Anaesthesia. Anaesthesia monitoring is continually improving. It is now done with a central venous pressure line and an intra-arterial line for continuous blood pressure measurement. Blood loss can occasionally be significant and brisk and the need to avoid or quickly correct sudden hypotension is obvious. This improvement in monitoring has probably helped to reduce the acute renal dysfunction occasionally seen when more prolonged episodes of hypotension were noted. Fresh frozen plasma (FFP) and platelets are used if coagulation problems occur in association with multiple transfusions. FFP is usually given if more than 6 units of blood are transfused.

Fluid management. A large increase in antidiuretic hormone (ADH) often occurs during the procedure and may contribute to volume overload in the first 24 h post-operatively (Zabbo *et al.*, 1985). We therefore routinely give 10 mg frusemide at the end of the operation. Pulmonary and cardiac complications appear to be lessened with this approach. Routine digitalis is not used on the assumption that it is not needed in patients with normal cardiac function as long as volume status is optimised.

Technical aspects. A reproducible, systematic plan for the operation saves time and lessens the risk of omitting or having to repeat any of the steps in the procedure. Our technique was developed at the Memorial Sloan-Kettering Cancer Center (Montie, 1983, 1988). The particular method used is probably less important than the experience of the operative team.

In this series there were no urinary leaks. An end-to-side anastomosis with spatulation of the ureter was generally used for ureterointestinal anastomosis. Internal stents were rarely used. A 2-layered closure was used, the first layer being interrupted 5/0 chromic catgut stitches. The second layer of interrupted 5/0 non-absorbable sutures between the seromuscular tissue of the bowel and the ureter tends to invert and reinforce the initial layer. Care was taken to ensure that during mobilisation of the ureter, a large amount of periureteric adventitial tissue was maintained in order to optimise the ureteric blood supply and to prevent ischaemic injury to the distal ureter.

There was 1 bowel leak. This occurred in a patient who had had 50 Gy of mixed beam radiation therapy pre-operatively to an extremely large pelvic field. This patient also developed a post-operative bowel obstruction requiring reoperation and died 2 years post-operatively of multiple enteric fistulas secondary to radiation enteritis. The only other bowel obstruction needing reoperation was in a patient who had had 6 courses of pre-operative M-VAC (methotrexate, vinblastine, Adriamycin and cisplatin). The infrequent use of pre-operative radiation therapy has probably contributed to this low incidence of bowel complications.

Several methods of draining the pelvis were used. The initial approach was to leave no drains at all; this was later changed to using large calibre drains that also irrigated the pelvis for 24 to 48 h. In more recent years, only closed-suction Jackson Pratt drains have been used in the pelvis and these are left for 3 to 4 days. The method of draining the pelvis, or even the need to drain the pelvis, remains open to debate.

Post-operative care

Cardiovascular. During the first few days after surgery there is probably a greater tendency to fluid overload than to volume depletion. On the third or fourth day the patient often needs an additional dose of diuretic. Early ambulation and aggressive respiratory therapy are included. Routine anticoagulation was not used. Low dose "Mini-Heparin" was given to some patients judged to be at high risk of developing embolic complications or to patients in whom another complication delayed recovery. There is some evidence to suggest that low dose heparin can increase the lymphatic flow, which may be undesirable. More recently, pulsatile anti-embolism stockings (PAS) have been used to reduce the risk of deep venous thrombosis.

Technical. An indwelling catheter sutured to the skin or ileostomy rod is left in the conduit for 1 week to keep the conduit decompressed. A loop stoma is routinely used because it provides a more reliable blood supply to the stoma, especially in obese or previously irradiated patients. Enterostomal therapy support is a necessity.

A common but not necessarily serious complication noted in an earlier review was a superficial wound separation, generally without evidence of infection (Wood *et al.*, 1987). As a result, skin staples are now generally left in place until the patient is ready for discharge.

The aim in caring for the cystectomy patient is to avoid the first complication, which can often lead to other more serious problems. Major complications after the initial procedure are dangerous to the patient and extremely costly (Mason and Garcia, 1984). An example of the importance of avoiding the initial complication is the consequence of a urine leak. While this may heal spontaneously, or following the addition of percutaneous nephrostomies, the patient is exposed to other problems such as ileus, respiratory problems secondary to fluid accumulation in the abdomen, or difficulty in fluid management, thromboembolic events secondary to an increased inflammatory response in the abdomen, infections and nutritional problems.

It is obvious that all complications cannot be avoided; in this case the goal must be early recognition to minimise the adverse effects. For example, strict attention to the patient's postoperative volume status is essential. Early congestive heart failure noted on a physical examination will be much easier to treat than when the patient develops more florid congestive heart failure, arrhythmia or myocardial infarction.

Major progress in the treatment of invasive bladder cancer will probably require innovations in chemotherapy. For the present, however, the early application of aggressive treatment in patients with potentially lethal cancers requires that treatment be safe and rehabilitation be as good as possible.

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Characterisation of Human Prostatic Adrenoceptors using Pharmacology Receptor Binding and Localisation

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Summary—Benign prostatic enlargement is a common cause of bladder outlet obstruction. Recent work has demonstrated the important role played by the sympathetic nervous system in the control of prostatic muscle tone. Although isometric muscle strip studies and clinical trials have highlighted the influence of alpha-1 adrenoceptors, radioisotope ligand binding studies have demonstrated a relatively increased density of alpha-2 adrenoceptors in the muscle within prostatic tissue, the significance of which is as yet unexplained.

Forty patients entered a study using pharmacological muscle strip experiments, radioligand binding assays and receptor autoradiography. Pharmacological data from these studies confirmed that contraction of prostatic muscle is mediated predominantly by alpha-1 adrenoceptor stimulation, with no evidence of significant alpha-2 adrenoceptor or cholinergic mediated effects. Radioligand binding studies confirmed that there is a higher concentration of alpha-1 binding sites as contrasted to alpha-2 within normal prostate, but that this relationship approaches equity in adenomatous prostate.

Autoradiographic localisation demonstrated that alpha-1 adrenoceptor binding is predominant within prostatic stroma with only a small component of alpha-2 adrenoceptors in this compartment. This comprehensive study supports the suggestion that prostatic muscular contraction is controlled by the influence of the sympathetic nervous system acting via alpha-1 adrenoceptors. These findings support the therapeutic use of specific alpha-1 adrenoceptor blockade in the management of benign prostatic hyperplasia.

Benign hyperplasia of prostatic muscle and stromal tissues (BPH) is a well recognised age-related phenomenon in the post-pubertal male. Both clinical and post mortem studies have reported there to be at least a 30% incidence of BPH by the sixth decade (Hieble and Caine, 1986). The majority of patients with BPH do not seek medical advice. Even when troublesome symptoms ensue, the clinical course often remains static for many years and less than one-third of all patients who have prostatic symptoms actually require surgery (Ball *et al.*, 1981). The management of prostatic bladder outflow obstruction in an aging population is becoming an increasingly important part of routine urological practice. Although surgery will remain the mainstay of treatment in these patients, medical treatment has an important therapeutic potential. Such situations include patients on waiting lists for definitive surgery who require symptomatic relief during the waiting period. Medical treatment is also required as a prophylactic measure in patients at risk of developing acute retention and where surgery is either contraindicated or not indicated on objective grounds despite the presence of symptoms.

Recent work has suggested that nearly 50% of prostatic outflow obstruction is mediated via the sympathetic component of the autonomic nervous

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system and is potentially reversible. The recognition of this "dynamic" component acting via the stimulation of alpha-1 adrenoceptors (Furuya *et al.*, 1982) has renewed interest in the therapeutic potential of alpha-adrenoceptor antagonists (Caine, 1986a, b). The importance of sympathetic influences is reinforced by the variations in symptom severity that accompany spontaneous modifications in sympathetic nerve traffic occasioned by cold and bladder distension and the observation that alpha-adrenoceptor agonists (in nasal decongestants and cold remedies) may induce acute retention in prostatic patients. Initial experience with the alpha-1/alpha-2 antagonist phenoxybenzamine was disappointing, in view of the unacceptably high incidence of side effects. However, recent studies have subdivided prostatic adrenoceptors into alpha-1 and alpha-2 subgroups (Lepor and Shapiro, 1984; Shapiro and Lepor, 1986). It has been suggested both on the basis of *in vitro* studies (Hieble *et al.*, 1985) and clinical trials (Kirby *et al.*, 1987) that stimulation of alpha-1 adrenoceptors is the main mechanism by which the sympathetic nervous system produces contraction of prostatic muscle (Kunisawa *et al.*, 1985). Recent work using ligand binding techniques has reported an increase in the density of alpha-2 receptors as compared with alpha-1 receptors in the adenomatous prostate (Hedlund *et al.*, 1985), for which no satisfactory explanation has so far been advanced. It was the intention of this combined receptor binding and isometric muscle strip study to resolve this paradox, in a multidisciplinary study, using pharmacological, biochemical and histochemical techniques.

Materials and Methods

Prostatic tissue specimens were obtained from 40 male patients with full informed consent, mean age 69 ± 2.2 years (95% confidence limits 65.44–74.09); 31 patients underwent transurethral resection of the prostate and 6 underwent retropubic prostatectomy as surgical treatment of urodynamically proven bladder outflow obstruction. Three patients (aged 44, 66 and 80 years) underwent radical cysto-urethrectomy for carcinoma; they had not been treated with radiotherapy and were considered to be controls, there being no clinical, urodynamic or histological evidence of bladder outlet obstruction.

In the patients undergoing transurethral surgery the tissue resected from the lateral lobes was subdivided into central and peripheral components. A loop resection of the central adenomatous prostatic tissue was performed and the bladder washed out, allowing collection of this tissue. This was followed by biopsy of the peripheral tissue in a similar manner. The prostate specimens were obtained from men with no recent exposure to drugs which influence sympathetic neurones.

Functional muscle strip studies

Strips of prostatic tissue approximately 1 cm × 1 mm were cut under the dissecting microscope, allowing portions with a significant number of fibres running in one direction to be selected. They were then suspended in 15 ml organ baths. The tissues were bathed in Krebs solution of the following composition (mM): NaCl 133, KCl 4.7, $NaHPO_4$ 1.3, $NaHCO_3$ 16.3, $MgSO_4$ 0.61, glucose 7.8 and $CaCl_2$ 2.52 (Bulbring, 1953). The solutions were gassed continuously with 95% oxygen and 5% CO_2 and maintained at 37°C. The tissues were placed under an initial resting tension of 0.5 g and allowed to equilibrate for 60 min. Changes in isometric tension were recorded by means of a force displacement transducer (Grass FTO3C) and displayed on a Grass polygraph (model 7D).

Cumulative dose response curves were constructed for noradrenaline (alpha-1 and alpha-2 agonist), phenylephrine (alpha-1 agonist) and UK-14,304 (alpha-2 agonist). Prazosin and rauwolscine were employed as selective alpha-1 and alpha-2 adrenoceptor antagonists respectively and pA2 values determined by the method of Arunlakshana and Schild (1959). The effectiveness of cholinergic stimulation, using acetylcholine as an antagonist, was investigated. Electrical field stimulation was carried out using two platinum ring electrodes suspended 1 cm apart. Pulse trains (0.5 ms duration, 60 V) were delivered using a Digitimer D4030 and isolated stimulator DS2. The prostatic strips were stimulated over a range of frequencies (2–50 Hz) with a 5-min interval between each stimulation. The consequences of pre-incubation with prazosin (10^{-7} M) or atropine (10^{-7} M) for 30 min were investigated. Tetrodotoxin 10 µl/10 ml was used to abolish all neurally mediated responses to electrical stimulation.

Radioligand binding experiments

Homogenates. Prostatic tissue from each patient was minced and homogenised with a Polytran homogeniser (maximum speed for 20 s) in ice-cold buffer containing 50 mM Tris-HCL (pH 7.6 at 25°C). The homogenate was centrifuged at 39,000 g for 20 min at 4°C and the pellet obtained resuspended in fresh buffer and recentrifuged twice more. The final pellet was resuspended in fresh

50 mM Tris-HCl buffer and stored at −70°C until used.

Saturation analysis

Saturation analyses were performed at several different concentrations of both (^{3}H)-prazosin (0.05–20 nM) and (^{3}H)-UK-14,304 (0.1–50 nM), for estimating alpha-1 and alpha-2 adrenoceptors respectively. Several tissues were also examined using ^{3}H-rauwolscine to estimate alpha-2 adrenoceptors. Total binding was determined in 1.0 ml volume containing 800 µl of membrane protein (300 g/tube), 100 µl of each (^{3}H)-ligand at varying concentrations, and 100 µl of 50 mM Tris/HCl buffer (pH 7.6). Non-specific binding was determined in 1.0 ml, containing 800 µl of tissue homogenate, 100 µl of 10^{-5} M phentolamine and 100 µl of each (^{3}H)-ligand at varying concentrations. Total and non-specific binding were determined in triplicate whenever possible. The assays were terminated by filtration through Whatman GF/B glass fibre filters, using a Brandel cell harvester. The filter discs were then rinsed with 3 × 3 ml of buffer (4°C). The glass filter discs were placed in 3 ml of scintillation fluid (Ecoscint). The scintillation vials were then counted in an LKB scintillation counter.

Radioligand receptor binding methods: autoradiographic localisation of receptors

Tissue preparation. A portion of each fresh prostate gland obtained from 10 men with BPH was freed of fat and connective tissue and placed directly on to cold microtome chucks, mounted in Tissue Tek 11 O.C.T. and frozen in liquid nitrogen-cooled isopentane. Serial sections were cut (10 µm) on a cryostat and mounted on to acid-washed, subbed microscope slides. These sections were air-dried for 2 h and then stored at 4°C.

Autoradiography

The technique for autoradiographic localisation of receptors first described by Young and Kuhar (1979) was used to study localisation of alpha-1, alpha-2 adrenoceptors and muscarinic adrenoceptors in the prostate.

The slide-mounted tissue sections were brought to room temperature. Labelling conditions for each of the receptor populations studied are described in Table 1.

All labelling was carried out at 25°C and labelled sections were placed in apposition to nuclear emulsion-coated coverslips (Ilford K2) and exposed at 4°C for 12 to 20 weeks (^{3}H)-prazosin, (^{3}H)-rauwolscine) or 5 to 10 weeks (^{3}H-QNB). After exposure, autoradiographic images were developed in D19 and fixed in Hypam. The sections were stained with toluidine blue whilst ensuring that the autoradiographic coverslips were not displaced.

Analysis of binding

The autoradiographs were examined by two independent observers and at the end of the study the results were combined. Serial sections for 10 patients were labelled with (^{3}H)-prazosin, (^{3}H)-rauwolscine and (^{3}H)-QNB respectively, thus enabling the same tissue area to be analysed and compared for both ligands. This minimised errors introduced if stromal areas of different muscle cell content had been measured.

Materials

(^{3}H)-prazosin, specific activity 82 Ci/mmol (New England Nuclear); (^{3}H)-rauwolscine, specific activity 88.7 Ci/mmol (New England Nuclear); (^{3}H)-UK-14,304, specific activity 85.5 Ci/mmol (New England Nuclear); (^{3}H)-QNB, specific activity 39 Ci/mmol (Amersham International); phento-

Table 1 Summary of Experimental Details for Slide-mounted Autoradiography

Binding site	*Radioligand*	*Pre-incubation*	*Incubation*	*Wash*	*Exposure period (weeks)*
Muscarinic	1-quinuclidinyl (phenyl-4-^{3}H) Benzilate	—	2 h PBS 1 nm ^{3}H-QNB ± 1 µM atropine	2 × 5 min PBS (4°C)	5–10
Alpha-1	Prazosin (7-methoxy-^{3}H)	—	30 min 170 mm TRIS/HCl (pH 7.6) 2 nM (^{3}H) prazosin + 10 µmol/ml PMSF ± 10 µM phentolamine	1 min 170 mm TRIS/HCl (25°C) 2 × 5 min TRIS/HCl (4°C)	12–20
Alpha-2	Rauwolscine (methyl-^{3}H)	30 min Krebs + 10 µmol/ml PMSF	1 h Krebs 2 nM (^{3}H) Rauwolscine ± 10 µM phentolamine	2 × 5 min Krebs (4°C)	12–20

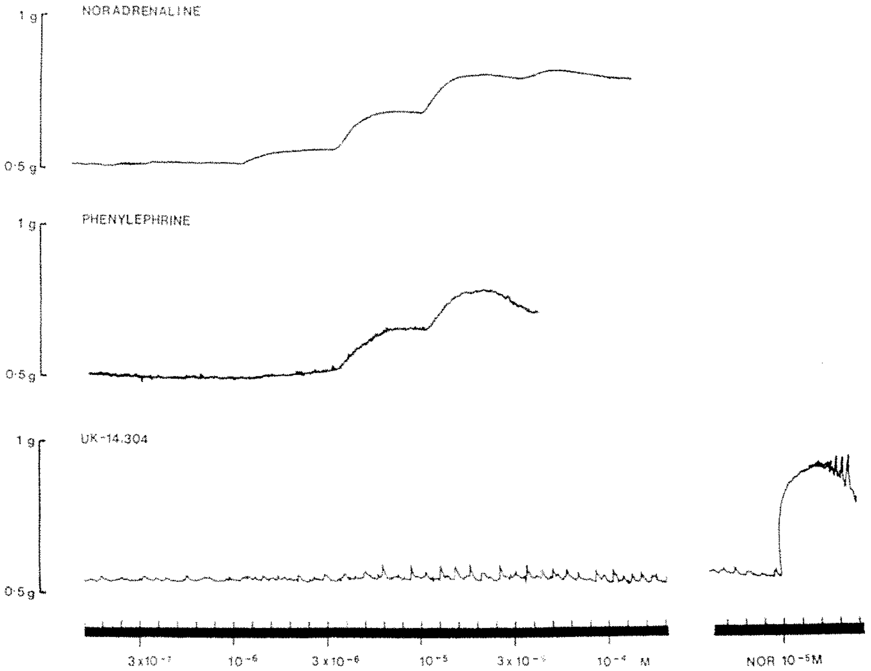


Fig. 1 Cumulative dose response curve to noradrenaline, phenylephrine and UK-14, 304.

lamine hydrochloride (Rogitine, Ciba-Geigy); phenylmethylsulphonylfluoride (Sigma); atropine sulphate (Antigen Ltd).

Results

Functional muscle strip studies

Noradrenaline and phenylephrine (3×10^{-7}–3×10^{-5} M) produced concentration-dependent contraction of both adenomatous and peripherally compressed and thereby more nearly "normal" prostate tissue preparations. The maximal response obtained with phenylephrine (alpha-1 agonist) was some 75% of that obtained with noradrenaline (alpha-1/alpha-2 agonist) (Fig. 1). The alpha-2 adrenoceptor agonist UK-14,304 studied over a concentration range of 10^{-7} to 10^{-4} M was without effect on all of the muscle strip preparations tested (Fig. 1). Prazosin (specific alpha-1 antagonist) was a potent competitive antagonist of noradrenaline-mediated contraction, producing parallel shifts to the right in the dose response curve but with no reduction in the maximum tension developed (Fig. 2). A Schild plot of these results (Fig. 3) confirms this with a pA_2 value of 9.1 and a slope of -0.9.

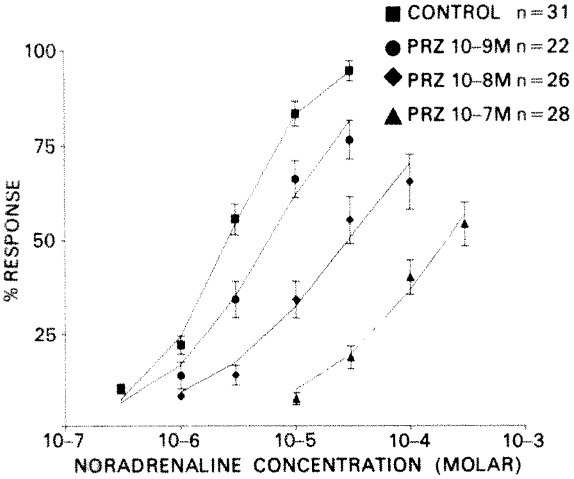


Fig. 2 Fitted dose response curves, contractile response to noradrenaline contrasting the response in the presence of differing concentrations of prazosin (10^{-9} M–10^{-7} M).

The alpha-2 adrenoceptor antagonist rauwolscine was less effective than prazosin in producing relaxation of prostatic strips that had been precontracted with noradrenaline. Rauwolscine applied at a concentration of 10^{-9} M resulted in only a small parallel shift to the right of the noradrenaline dose response curve consistent with the known selective alpha-2 antagonist activity of this compound (Fig. 4). However, at high concentrations (10^{-8} M and 10^{-7} M) the top of the noradrenaline dose response curve was shifted. This finding is

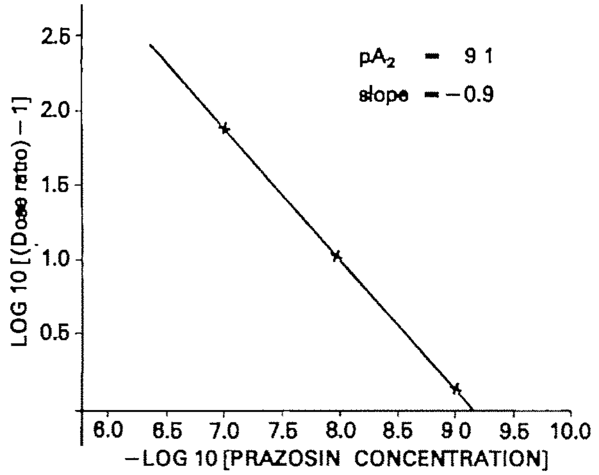


Fig. 3 Schild plot for prazosin in central prostate

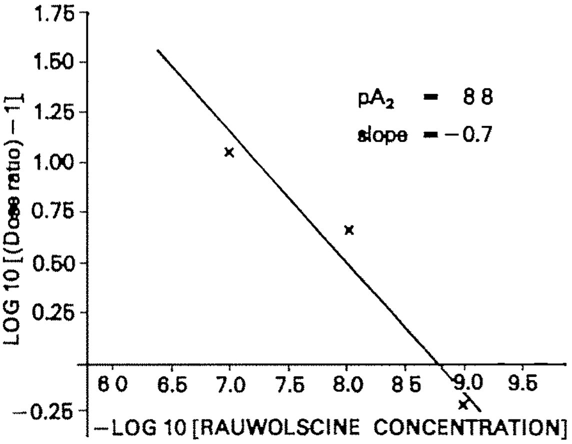


Fig. 5 Schild plot for rauwolscine in central prostate.

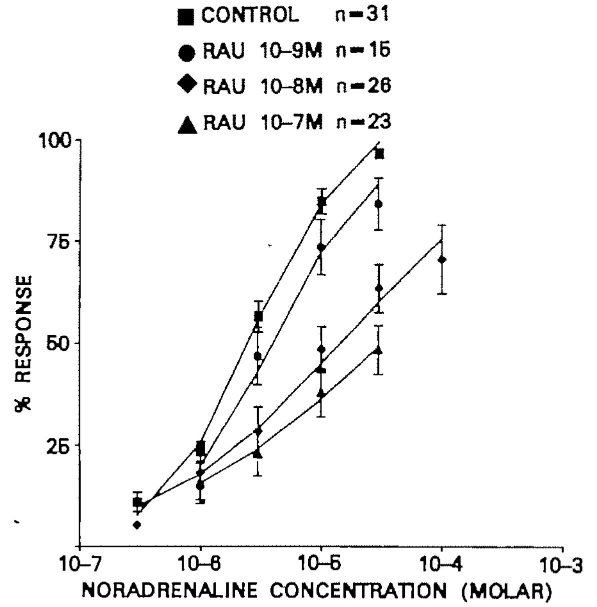


Fig. 4 Fitted dose response curves, contractile response to noradrenaline in the presence of differing concentrations of rauwolscine (10^{-9} M–10^{-7} M)

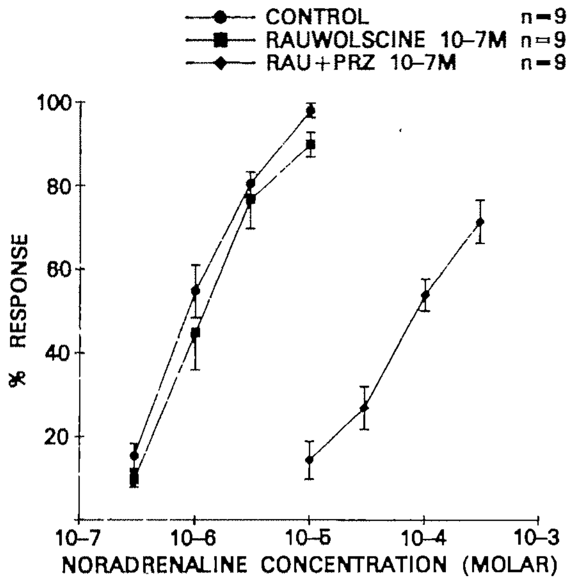


Fig. 6 Fitted dose response curves contrasting the effect of rauwolscine 10^{-7} M and combined rauwolscine and prazosin 10^{-7} M on the contractile response to noradrenaline.

consistent with a recognised action of rauwolscine as an alpha-1 antagonist when it is present in high concentration. A Schild plot of these results revealed a pA$_2$ of 8.8 but with a poor slope (−0.7), inconsistent with a competitive action on alpha-2 adrenoceptors (Fig. 5).

The effect of rauwolscine on the dose response curve to noradrenaline when applied to a preparation of adenomatous prostate is shown in Figure 6. Rauwolscine 10^{-7} M caused only a modest shift to the right of the dose response curve. However, when prazosin 10^{-7} M was added to the bath and the response to noradrenaline repeated, an additional substantial shift occurred, suggesting that the response was mediated via alpha-1 adrenoceptors in this tissue. A similar study is shown in Figure 7, in which prazosin was added first and rauwolscine second. Rauwolscine caused only a modest additional shift to the right of the dose response curve, confirming that alpha-2 adrenoceptor-mediated contraction of hyperplastic prostatic tissue was of minimal importance.

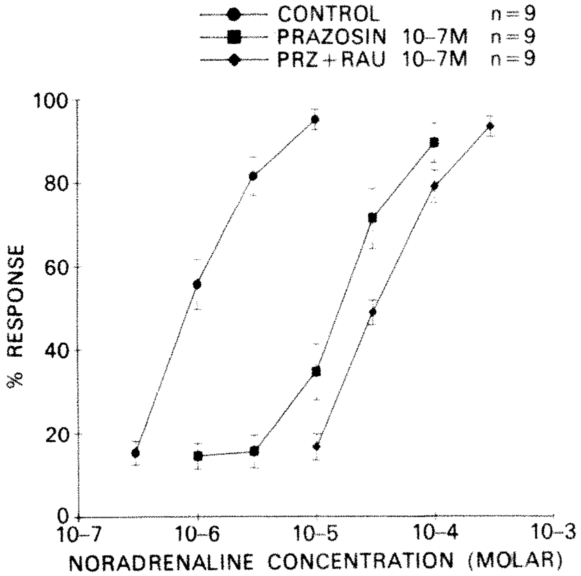


Fig. 7 Fitted dose response curves contrasting the effects of prazosin 10^{-7} M and combined prazosin and rauwolscine 10^{-7} M on the contractile response to noradrenaline.

The application of acetylcholine did not produce consistent contractile responses. Contractile response to nerve-mediated stimulation was largely abolished by pre-treatment with tetrodotoxin; a similar result was produced by incubation with prazosin, whereas atropine had little effect (Fig. 8).

Radioligand binding studies

Homogenates. Saturation analyses were carried out on tissue from adenomatous "central" prostate (7 patients), "peripheral" compressed largely non-hyperplastic prostate (8 patients) and normal "control" prostate (3 patients). The results of these studies are summarised in Table 2 and Figure 9. The binding of ^{3}H prazosin and ^{3}H UK14,304 was saturable and in each case a single class of binding sites was identified, as confirmed by a linear Scatchard analysis plot in each case. The equilibrium dissociation constants (K_D) ranged between 0.32 and 0.52 nM for alpha-1 receptors and 1.8 and 3.10 nM for alpha-2 receptors. (^{3}H-rauwolscine gave similar results). In some tissues it was not possible to measure alpha-2 binding sites but alpha-1 receptors were always present in all of the tissues examined. If alpha-1 receptors were detected, the results for alpha-2 receptors were included in the analyses. In contrast, if both alpha-1 and alpha-2 receptors were absent, the tissue was discarded, as it was presumed to be damaged. The adrenergic receptor concentration (B_{MAX}) was calculated in fmol/mg protein. The range of values measured was 61.1 to 79.4 fmol/mg protein for alpha-1 binding sites and 12.1 to 36.1 fmol/mg protein for alpha-2 binding sites. Figure 9 contains representative Scatchard analysis curves for "peripheral" prostate, but similar patterns were also obtained with both "central" and "normal" prostate. This is evidenced by the correlation coefficients for the representative curves; "control prostate" (^{3}H) prazosin $r=-0.96$, (^{3}H) UK14,304 $r=-0.94$; "peripheral prostate" (^{3}H) prazosin $r=-0.97$ (^{3}H) UK14,304 $r=-0.89$; "central prostate" (^{3}H) prazosin $r=-0.98$ (^{3}H) UK14,304 $r=-0.92$. The ratio of alpha-1 to alpha-2 receptors was approximately 2:1 in adenomatous central prostate and 4:1 in peripheral non-adenomatous tissue. Statistical comparison of these data, using the Mann

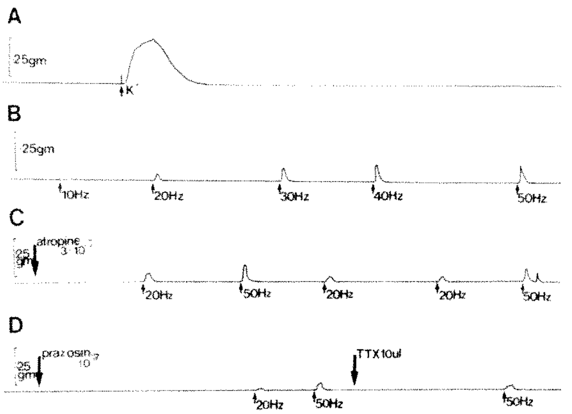
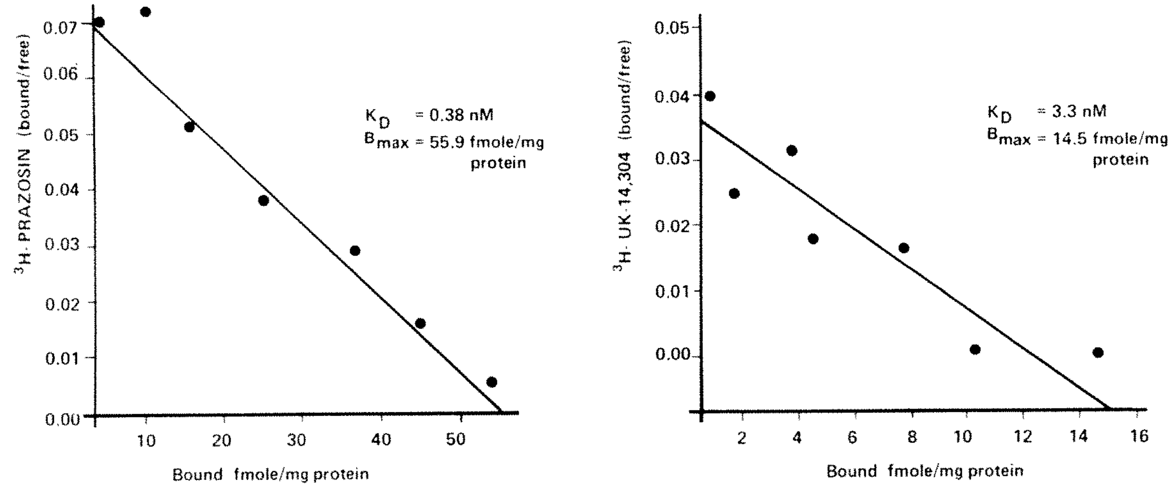


Fig. 8 (A) Response to maximal stimulation with K$^+$. (B) Response to nerve stimulation. (C) Effect of pre-incubation with atropine 3×10^{-7} M on the response to nerve stimulation. (D) A comparison of pre-incubation with prazosin 10^{-7} M and TTX on the response to nerve-mediated stimulation.

Table 2 Human Prostate Tissue: Alpha-adrenoceptor Ligand Binding Studies

	^{3}H Prazosin α1		*^{3}H-UK-14,304 α2*	
Sample	K_D *(nM)*	B_{max} *(fmol/mg)*	K_D *(nM)*	B_{max} *(fmol/mg)*
Prostate (BPH) (central) n=7	0.51 ±0.07	65.9 ±5.2	2.34 ±0.26	36.1 ±6.2
Prostate (BPH) (peripheral) n=8	0.32 ±0.03	79.4 ±11.1	3.10 ±1.0	18.4 ±3.1
Prostate (Control) n=3	0.52	61.1	1.8	12.1

The above results represent the mean ± S.E.M. from separate experiments performed in triplicate.



A. Scatchard Analysis ^{3}H- PRAZOSIN $\alpha 1$

B. Scatchard Analysis ^{3}H- UK-14,304 α 2

Fig. 9 Representative curves from peripheral prostate demonstrating Scatchard analyses for ^{3}H prazosin (A) and ^{3}H UK-14,304 (B).

Whitney U statistic, confirmed a significant difference between alpha 1 and alpha 2 receptor binding sites in the peripheral prostate ($P = 0.0014$; 95.9% C.I. 35.82). Conversely, the apparent difference between alpha 1 and alpha 2 receptors for central prostate failed to reach significance ($P = 0.1252$; 95.9% C.I. −8.71).

Autoradiographic localisation of receptors

Alpha-1 binding sites were localised mainly to the stroma of the prostate with a clear predominance over alpha-2 binding sites (Fig. 10E). Although on the basis of this work, specific localisation to the muscular stroma was not possible, the alpha-1 binding sites evident were more likely to be related to smooth muscle than fibroblasts or collagenous connective tissue. Computerised quantitative assessment of this material revealed a ratio for the adrenoceptors of alpha-1 : alpha-2 which was 4:1. Alpha-2 binding sites were related principally to blood vessels with a significant but less dense distribution in the muscular stroma and associated with the basement membrane of glandular epithelium (Fig. 10B). Muscarinic cholinoceptor binding sites were confined almost exclusively to the glandular epithelium (Fig. 10F). These findings represent part of a larger and more comprehensive analysis of the receptor populations within adenomatous prostatic tissue, which is reported elsewhere (James *et al.*, 1988).

Discussion

The human gland is innervated by "short" adrenergic sympathetic nerves whose cell bodies lie in the pelvic plexus (Baumgarten *et al.*, 1968), cholinergic parasympathetic nerves and peptidergic nerves (Gu *et al.*, 1983). Despite the clinical importance of the prostate gland, few comprehensive studies of the innervation and ultrastructure of the prostate have been reported. It has been suggested that although there is dual innervation, the glandular acini are principally supplied with secretomotor cholinergic parasympathetic nerves and the predominant motor control of prostatic muscle is by adrenergic neurones (Gosling, 1983). It is likely that there is an important local synaptic interaction between cholinergic and adrenergic neurones, as reported from the adjacent bladder neck region (Nergardh, 1975; Mutoh *et al.*, 1987). This concept has, however, been challenged by Vaalasti and Hervonen (1980), who dispute the suggestion that there is a significant sympathetic or parasympathetic nerve supply to acinar epithelium.

Dunzendorfer *et al.* (1976) reported that there is a reduced innervation of adenomatous in contrast to normal prostate, affecting both the cholinergic and adrenergic components. An explanation for this observation is that there is a dilution of neural structures by the marked increase in muscular and, to a lesser extent, glandular components in the hyperplastic gland (Bartsch *et al.*, 1979). This

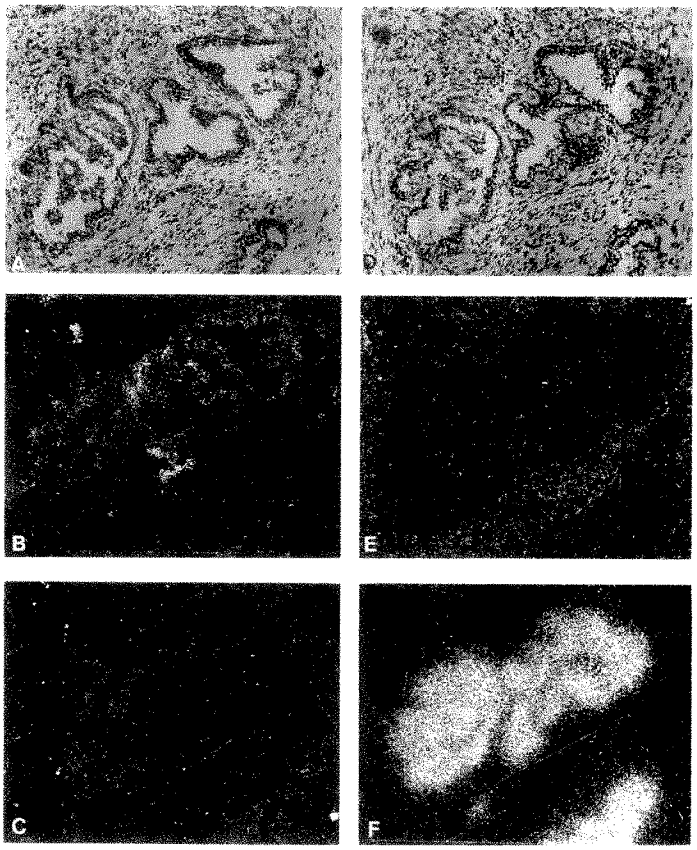


Fig. 10 Ten micron sections of adenomatous human prostate. A/D Toluidine blue stained sections relating to figures B and C/E and F, demonstrating glandular acini in a fibromuscular stroma. (B) binding for alpha-2 adrenoceptors. (C) control. (E) binding for alpha-1 adrenoceptors. (F) binding for muscarinic cholinoceptors.

observation is supported by pharmacological isometric studies which demonstrate an exaggerated response of hyperplastic as compared to normal prostatic tissue to adrenergic agonists, compatible with a post-junctional supersensitivity (Kitada and Kumazawa, 1987).

The third group of neurones contain putative peptide neurotransmitters. Although they have been alluded to in the literature, detailed characterisation of their distribution has not yet been reported. Studies which we have carried out reveal the presence of vasoactive intestinal peptide (VIP), neuropeptide Y (NPY), somatostatin, substance P and calcitonin gene related peptide (CGRP) in nerves and ganglia within the prostate (Crowe and Chapple, unpublished work). The precise role of these neurones is at present obscure, although (based on other observations) it is likely that they have an important function in controlling vascular tone and may be of importance in neuromodulation, since VIP and NPY are known to be present within cholinergic and adrenergic neurones (Burnstock, 1986).

Learmonth (1931) reported that stimulation of the pre-sacral nerve in man contracted the prostatic musculature. Since then, urethral pressure profile studies (Donker *et al.*, 1972) and *in vitro* isometric prostatic strip studies (Caine, 1986a) have confirmed the important influence of the sympathetic nervous system on the bladder outflow tract and raised the possibility of pharmacological treatment by alpha blockade. Initial experience with the non-selective alpha antagonist phenoxybenzamine was disappointing because of the unacceptably high incidence of side effects, attributable to the blockade of alpha-2 receptors and subsequent interference with the negative feedback control of the release of noradrenaline. With recognition of the importance of the alpha-1 receptor in mediating sympathetic action in the normal and adenomatous prostate, attention has turned to the therapeutic use of selective alpha-1 antagonists such as prazosin (Shapiro *et al.*, 1981), with the intention of reducing unwanted side effects. Although numerous pharmacological isometric studies have been reported in the literature, only one study has also investigated normal prostatic tissue (Hedlund *et al.*, 1985). Ligand binding techniques have only recently been applied to the investigation of human prostatic alpha-1 and alpha-2 adrenoceptors. These studies have raised an as yet unexplained paradox, one study demonstrating an excess of alpha-2 over alpha-1 receptors in adenomatous prostate despite a demonstrable functional predominance of alpha-1 receptors (Hedlund *et al.*, 1985) and the other suggesting equivalent densities for both groups of alpha receptors (Lepor and Shapiro, 1984; Shapiro and Lepor, 1986). It has been suggested that alpha-2 receptors may have an important role in mediating contraction of canine prostatic muscle (Shapiro *et al.*, 1987), but care needs to be exercised in the extrapolation from animal models to man.

The results of the isometric studies reported here confirm that there is a functional predominance of alpha-1 adrenoceptors in human prostatic muscle. The limited inhibition by alpha-2 antagonists of *in vitro* prostatic muscle contraction confirms these findings and we report the first use of the specific alpha-2 agonist (UK 14,304) on human prostatic tissue. The results of radioligand studies confirm the trend towards an increase in alpha-2 binding sites towards parity in adenomatous tissue reported by previous studies, but demonstrate an overall predominance of alpha-1:alpha-2 receptors of approximately 3:1 which is in accordance with the results of the functional studies. A potential source of error would be if there were significant differences in innervation and histological structure between different areas of the same gland. We have investigated this possibility by examining tissue from a number of different areas within prostatic adenomata removed at the time of open operation and although there was significant regional variation, this appeared to be occurring randomly with no clearly identifiable regional trends.

It is evident that anatomical, functional isometric and ligand binding studies are in agreement in suggesting that contraction of prostatic smooth muscle occurs in response to sympathetic stimulation acting principally via alpha-1 receptors. Confirmatory proof has, however, awaited the specific localisation of binding sites by autoradiographic techniques. The specific localisation of neural receptor binding sites within human prostate has only previously been reported for muscarinic cholinoceptors (Lepor and Kuhar, 1984; Hedlund *et al.*, 1985). These are located predominantly in the epithelium of glandular acini at a concentration 70-fold higher than in the prostatic stroma. This finding has been confirmed by our experimental results. Alpha-1 binding sites are, as expected, localised predominantly to the prostatic stroma, where they are most likely to be associated with muscle. Indeed they are present in a concentration which is approximately 4 times higher than corresponding alpha-2 binding sites (James *et al.*, 1988). The presence of alpha-2 receptors in the muscle layer would be compatible with their proposed presynaptic role in modulating a negative feedback pathway to control the release of the neurotransmitter noradrenaline. The highest concentration of alpha-2 binding sites was in close association with blood vessels, with a significant presence on the basement membrane of glandular epithelium, suggesting that their primary role is likely to be related to the control of vascular tone, with additional importance in secretomotor function.

This study, by using a combination of investigative techniques, has demonstrated the pathway whereby sympathetic stimulation produces prostatic muscular contraction. These results fully underwrite the use of alpha-1 adrenoceptor antagonists in the provision of symptomatic relief to selected patients with benign prostatic hyperplasia. Further work should be aimed at the investigation of whether there are prostate-specific alpha-1 adrenoceptors, which will allow the further refinement and tailoring of more effective symptomatic treatment for prostate obstruction.

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^{99m}Tc-Nanocolloid Bone Marrow Scintigraphy in Prostatic Cancer

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Summary—Bone marrow scintigraphy was performed in 23 patients with histologically proven carcinoma of the prostate, using a new radiopharmaceutical, Technetium-99m nanocolloid. The results suggest that although bone marrow scintigraphy is less sensitive than conventional bone scintigraphy in the detection of skeletal metastases from prostatic carcinoma, the technique may have a place in the management of patients with advanced metastatic disease, especially those who are anaemic, by identifying those patients at risk from myelosuppressive therapy.

Technetium-99m methylene diphosphonate (^{99m}Tc MDP) bone scintigraphy is a standard technique used in the assessment and management of patients with prostatic cancer (McKillop, 1986). Positive bone scintigraphy occurs in advanced disease, but conventional bone scans indicate only the extent of cortical bone involvement. It has been suggested that bone marrow scintigraphy might provide proof of metastatic spread in prostatic cancer patients at an earlier stage than can be detected by conventional bone imaging (Ito *et al.*, 1973). However, because of the limitations of the radiopharmaceuticals previously available for bone marrow scintigraphy, the technique fell out of favour (Fordham and Ali, 1981). The development of new colloids which are more efficiently taken up by the marrow has produced a revival of interest in marrow imaging.

We have used bone marrow scintigraphy with ^{99m}Tc nanocolloid in 23 patients with prostatic carcinoma to determine whether the technique has a potential role in their management.

Patients and Methods

A series of 23 patients with histologically proven carcinoma of the prostate (mean age 67.3 years, range 53–91) required bone scintigraphy as part of routine assessment to determine the extent of disease during the study period: this group should not be seen as representing the full spectrum of the disease. In addition to a conventional bone scan using ^{99m}TcMDP (hereafter referred to as bone scan), and with informed consent, each patient underwent marrow scintigraphy using ^{99m}Tc-nanocolloid (hereafter referred to as marrow scan).

Three millilitres of ^{99m}Tc nanocolloid (supplied by Solco Nuclear), with an activity of 400 MegaBecquerels (MBq) were injected intravenously. An initial posterior pelvic scan was taken at 30 min, using a 40 cm gamma camera with low energy parallel hole collimator coupled to a small computer. The time taken to acquire 500,000 counts was noted and used for all subsequent images. Bone scans and marrow scans were assessed by two observers (H.W.G. and J.H.McK.) who were not in possession of clinical or radiological information.

Bone scans were reported as (a) normal, (b) suspicious but equivocal for metastases, (c) unequivocally positive for metastases or (d) markedly positive. Marrow scans were assessed for (a) distribution of active marrow throughout the skeleton, (b) degree of uptake of the radiopharmaceutical by the central marrow, (c) areas of photon deficiency ("cold spots") and (d) areas of photon richness ("hot spots").

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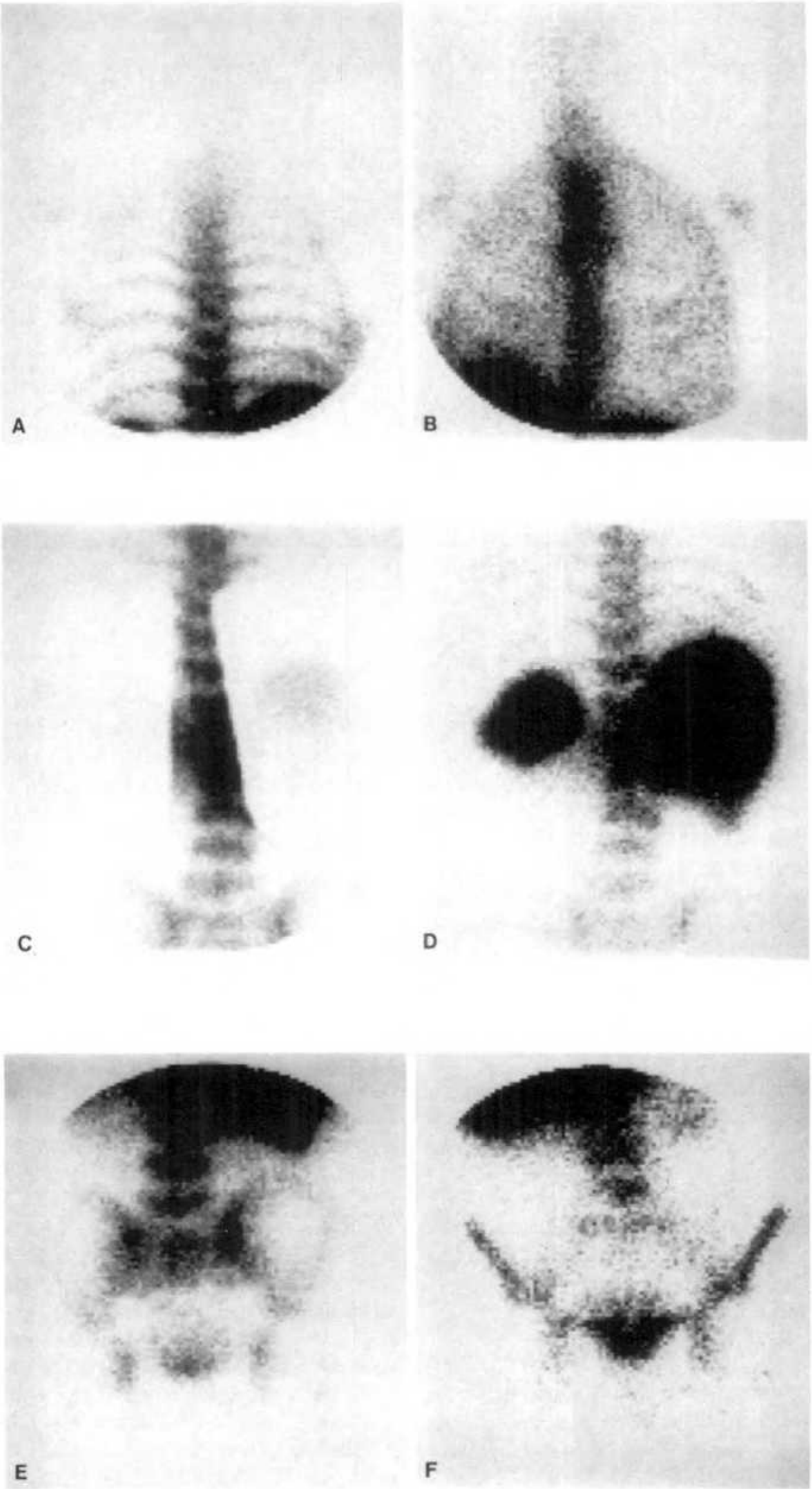
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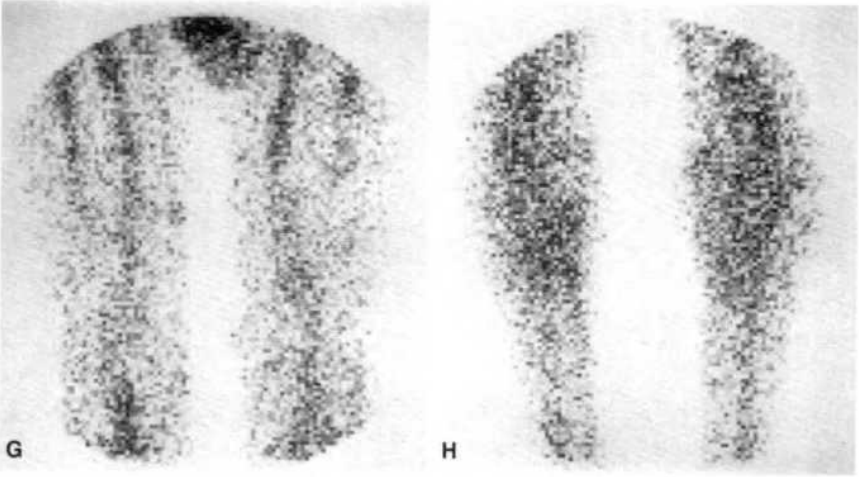

Fig. 1 Normal bone marrow scan. (A) Posterior thorax: normal uptake in vertebral column and ribs. (B) Anterior thorax: normal uptake in sternum. (C) Posterior abdomen: normal uptake in lower thoracic and lumbar vertebrae with liver and spleen shielded out. (D) Posterior abdomen: as (C) without shield. (E) Posterior pelvis: normal uptake in lower lumbar vertebrae, sacrum, sacroiliac joints and ischial tuberosities. (F) Anterior pelvis: normal uptake in iliac blades and pubic bones. (G) Both femora: no uptake in femora (blood pooling of activity in femoral vessels only). (H) Both tibiae: no uptake in tibiae or fibulae (blood pooling of activity in venous plexuses of calf only).

Results

Of the 23 marrow scans performed, 9 were normal. In a normal marrow scan, active marrow was present only in the central or axial skeleton with little or no extension into long bones; the uptake of radiopharmaceutical by the active central marrow was homogeneous (Fig. 1).

Fourteen patients had abnormal marrow scans with focal hot and/or cold lesions; 5 of these patients showed no tracer uptake in the central marrow with peripheral expansion of active marrow into the long bones (Fig. 2).

A total of 23 bone scans were performed, only 2 being completely normal; 5 bone scans were positive and 6 were markedly positive for metastatic disease; 10 bone scans were reported as suspicious of metastatic disease. In 7 of these, radiology revealed alternative non-metastatic explanations for the abnormal scans. In 3 patients with suspicious bone scans, radiology confirmed metastases.

Correlation of bone scans and marrow distribution

In all but 5 marrow scans, marrow distribution and uptake of the radiopharmaceutical by the central marrow was normal. The 5 patients with destruction of central marrow and peripheral expansion of marrow into the long bones all had markedly positive bone scans (Table 1).

Correlation of bone scans and focal marrow lesions

Table 2 compares the distribution of hot and cold lesions in the marrow scans with the bone scans. Of the 2 patients with normal bone scans, 1 exhibited a hot lesion on the marrow scan. Of the 10 patients with suspicious bone scans, 8 had normal marrow scans, 1 exhibited a hot lesion and 1 a cold lesion. Cold lesions occurred more commonly in patients with positive or markedly positive bone scans. Hot lesions on marrow scans were demonstrated in patients in all 4 bone scan groups.

On marrow scanning the liver and spleen take up radiopharmaceutical not accumulated by the bone marrow (Fig. 1D). This obscures the lower thoracic and upper lumbar spine but does allow evaluation of the liver and spleen for focal lesions. Cold liver lesions were seen in only 2 patients; both had markedly positive bone scans and grossly abnormal marrow scans.

Correlation of marrow scan findings and peripheral blood counts

An attempt was made to correlate retrospectively peripheral blood counts with marrow scan findings. Blood counts were available at the time of marrow scanning in 15 patients. All 8 patients with a haemoglobin greater than 11 g/dl exhibited normal marrow distribution (Table 3). All 5 patients with

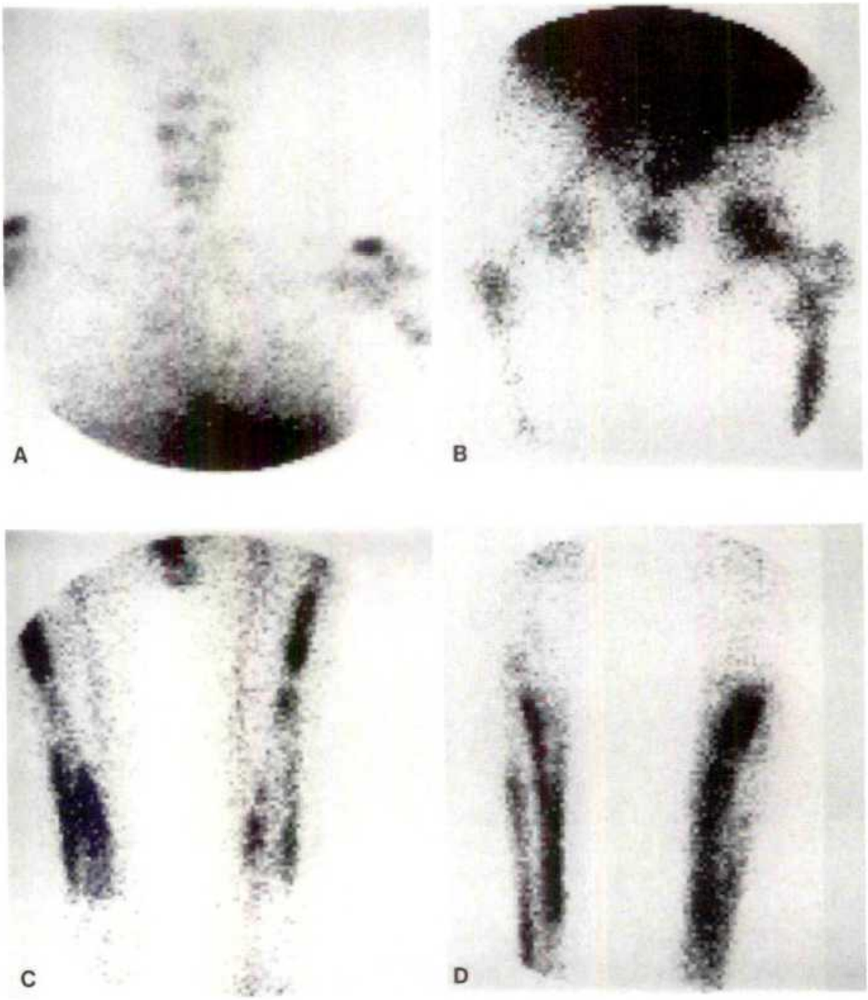

Fig. 2 Abnormal bone marrow scan. (A) Posterior thorax: absence of uptake in thoracic vertebrae and ribs; patchy uptake in cervical spine with "cold spots"; "hot spots" in both humeral heads (compare with Fig. 1(A)). (B) Posterior pelvis: patchy uptake in pelvis with extension of active marrow into both femora (compare with Fig. 1(E)). (C) Both femora: extension of active marrow into both femora (compare with Fig. 1(G)). (D) Both tibiae: extension of active marrow into both tibiae (compare with Fig. 1(H)).

Table 1 Comparison of Bone Scans and Marrow Distribution on Marrow Scans

	Marrow distribution	
Bone scan	*Normal*	*Abnormal*
Normal	2	—
Suspicious (negative radiology)	7	—
Suspicious (positive radiology)	3	—
Positive	5	—
Markedly positive	1	5

(Abnormal scans exhibited destruction of central marrow and expansion of active marrow into the peripheral skeleton).

central marrow destruction and marrow expansion on marrow scintigraphy were anaemic. Two patients with anaemia had normal marrow scans; both were found to have iron deficiency anaemia which responded to treatment.

A patient with severe metastatic disease was given systemic chemotherapy in standard doses. His haemoglobin was 10 g/dl and white cell count $53 \times 10^9/\text{mm}^3$ prior to treatment. He died 6 days later with profound leucopenia. His marrow scan, which was performed the day before chemotherapy was administered but not reported until after treatment, revealed no active central marrow

Table 2 Comparison of Bone Scans and Hot and Cold Lesions on Marrow Scans

	Lesions on marrow scan			
Bone scan	*None*	*Hot only*	*Cold only*	*Hot and Cold*
Normal	1	1	—	—
Suspicious (negative radiology)	6	—	1	—
Suspicious (positive radiology)	2	1	—	—
Positive	—	—	2	3
Markedly positive	—	—	5	1

Table 3 Comparison of Haemoglobin Levels and Marrow Distribution

	Marrow distribution	
Haemoglobin	*Normal*	*Central destruction/Peripheral Expansion*
>11 g/dl	8	—
<11 g/dl	2	5

(Fig. 3) with little functioning marrow in the distal long bones.

Discussion

Nanocolloid is derived from human serum albumin. Over 90% of its particles are less than 80 nm in diameter; this particle size has been shown to be optimal for phagocytosis by cells of the reticuloendothelial system in the marrow and should result in better imaging when labelled with radioisotopes. In experimental rat models, 15% of an injected dose of nanocolloid is taken up by the marrow compared with only 5% of human serum albumin millimicrospheres (Hotze *et al.*, 1986), 3.5% of Technetium-99m antimony colloid and 0.8% of Technetium-99m sulphur colloid (Martindale *et al.*, 1980); the remainder of the injected dose is taken up by the liver and spleen (Hotze *et al.*, 1986).

The distribution of the reticuloendothelial and haemopoietic components of bone marrow varies in some haematological diseases (Van Dyke *et al.*, 1967; Fordham and Ali, 1981). However, it is generally accepted that metastatic disease affects both components similarly, although there is little supportive evidence.

The ability to detect early metastatic lesions in bone marrow using nanocolloid has been demonstrated in some tumours, including malignant melanoma and thyroid carcinoma (Hotze *et al.*, 1986). These early metastases are seen as hot spots and similar hot spots might be expected to signify early metastases in prostatic cancer. Since only 2 patients in the present series had completely normal *bone* scans it is difficult to answer this point, but the predominant lesions in our series of *marrow* scans

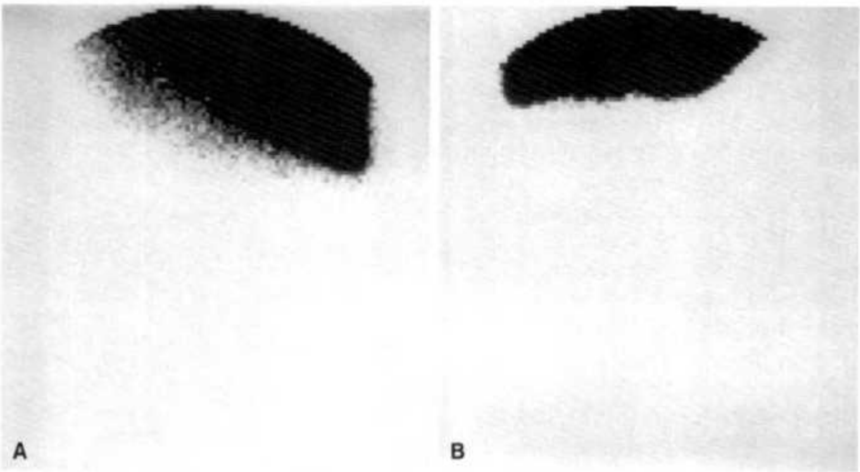

Fig. 3 Complete destruction of central marrow. (A) Posterior abdomen: absence of marrow activity in central skeleton (compare with Fig. 1(D)). (B) Anterior abdomen: as Fig. 3(A).

were cold spots. These cold spots occurred only in patients whose bone scan was positive, except for 1 cold lesion in a patient with an equivocal bone scan and negative radiology. Far fewer hot spots were seen on our marrow scans. The nature of these hot spots remains a matter for speculation at this stage, particularly since we have demonstrated hot spots in patients in all bone scan groups, including those with normal bone scans. We plan to undertake marrow scintigraphy in more patients with normal bone scans in an attempt to determine whether hot lesions might represent early metastatic disease in prostatic cancer. Destruction of central marrow and expansion of active marrow into distal long bones on marrow scintigraphy was seen only in patients with grossly abnormal bone scans. This suggests that marrow *destruction*, detectable by ^{99m}Tc-nanocolloid scans, occurs at a late stage in the disease process and only after cortical metastases are established. The fact that all of these patients were anaemic indicates the marrow destruction seen on scintigraphy to be clinically significant. Anaemia in patients with metastatic prostatic cancer is not necessarily due to marrow destruction by metastases and in 2 of our patients bone marrow scintigraphy helped to identify coincidental treatable anaemias.

Bone marrow scintigraphy has been shown to be of value in other tumours where bone scanning was equivocal. Coakley *et al.* (1987) were able to reduce the number of equivocal bone scans from 23 to 4 in patients with breast and lung cancer and lymphoma. This has not been our experience in patients with prostatic cancer because marrow scintigraphy was, in almost all cases, positive only when the bone scan was very abnormal.

The death of one of our patients following chemotherapy might indicate an important role for marrow scintigraphy. Bone marrow scintigraphy may allow the clinician to identify patients at risk from fatal marrow suppression following systemic chemotherapy and total body irradiation and may become an essential investigation in patients being considered for potentially myelosuppressive treatment. Furthermore, the development of ^{89}Strontium (^{89}Sr) as a therapy for patients with advanced carcinoma of the prostate (Robinson *et al.*, 1987) may provide an ideal treatment for patients with extensive bone marrow destruction and peripheral marrow expansion. Since irradiation of the bone marrow by ^{89}Sr is limited to those areas with extensive metastases, marrow extension into the long bones may well escape irradiation. Bone marrow scintigraphy may have a role in identifying patients suitable for this therapy. Work in this area is currently in progress.

Although bone scanning is a more sensitive indicator for skeletal metastases than bone marrow scintigraphy, it is concluded that bone marrow scintigraphy may have a role in the management of patients with metastases from carcinoma of the prostate. Currently, we would use bone marrow scintigraphy to identify patients at risk from myelosuppressive treatment and in patients with anaemia, since a normal scan would indicate an alternative, and possibly remediable, cause for the anaemia.

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Long-term Antibiotic Treatment of Chronic Bacterial Prostatitis. Effect on Bacterial Flora

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Summary—The bacterial flora in patients referred with chronic bacterial prostatitis were studied. Only 13% had Gram-negative bacteria in significant numbers but 43% had Gram-positives using the same criteria. Half of the patients were symptom-free by the end of a 12-week course of antibiotics and remained so after 6 months; in one-third the symptoms were unchanged 6 months after completing treatment. The relief of symptoms correlated with the disappearance of white blood cells in the expressed prostatic secretion (EPS) and with a lowered pH in the EPS.

Thus only 1 of the 14 patients without symptoms at 6 months had a significant growth of bacteria at the prostatic level, whereas 7 of 10 patients with unchanged symptoms had a significant bacterial colonisation. Although the initially infecting organism was eliminated in about half of the patients, new Gram-positive bacteria were isolated after treatment in 13 of 29 patients; 12 of these resolved spontaneously within 6 months. Five patients with Gram-positive bacteria were colonised with new Gram-negatives at the end of treatment. Two healed spontaneously but 3 remained colonised with Gram-negatives at the end of the follow-up period. These findings make it likely that many patients infected with Gram-positive bacteria benefit from antibiotic treatment. However, disturbances in the bacterial flora by antibiotic treatment may facilitate invasion by new types of bacteria.

Gram-negative bacteria are generally considered to be responsible for prostatitis (Meares and Stamey, 1968; Drach, 1974; Mårdh and Colleen, 1975; Smart *et al.*, 1976). Some authors consider Gram-positive organisms to be potential pathogens in prostatitis (Schmidt and Patterson, 1966; Drach, 1974; Blacklock, 1979; Giamarellou *et al.*, 1982) but others question this (Meares, 1980; Stamey, 1980; Pfau, 1983). Nevertheless, positive bacterial cultures are seldom obtained in patients with chronic prostatitis. The signs and symptoms of both bacterial and non-bacterial prostatitis are variable and inexact, making the two conditions clinically indistinguishable.

The purpose of the present investigation was to analyse the bacteriological findings in patients with symptoms of chronic prostatitis and to study the effect of antibiotic treatment on the bacterial flora in these patients. The diagnosis of prostatitis was based upon the criteria of Meares and Stamey (1968). In this study patients with both Gram-negative and Gram-positive organisms on culture were investigated and treated.

Patients and Methods

A total of 122 men (mean age 36 years) were referred to the Department of Urology with a diagnosis of chronic prostatitis. All had previously been treated with antibiotics, though not during the last month prior to this investigation. Of these, 33 consecutively diagnosed as having bacterial prostatitis according to the culturing method described by Meares and Stamey (1968), but including patients with a significant count of Gram-negative or Gram-positive organisms in the expressed prostatic secretion, were entered into the study. Thus the bacterial count in the EPS exceeded that in the first voided portion of bladder urine (VB1) and midstream urine (VB2) by at least 10 times;

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10 μl of EPS were collected by a micropipette, inoculated on the plate and spread by rotating glass beads. Only plates with >30 colonies were recorded. If necessary, samples were diluted and calculations done accordingly. Only patients with $\geqslant 10 \times 10^3$ bacteria/ml EPS were thus included. The bacterial flora in these patients were predominantly sensitive to both co-trimoxazole and cephadroxil and the patients were treated with antibiotics over a limited period (12 weeks). Patients were randomly allocated in a double-blind manner to receive either cefadroxil 1g *bd* (Cefamox, Bristol) or co-trimoxazole (160 mg trimethoprim, 800 mg sulphamethoxazole) *bd* (Eusaprim forte, Burroughs Wellcome). Treatment was commenced within 1 week of the diagnosis.

Sixteen men (mean age 29 years) without signs or symptoms of prostatitis served as controls.

Clinical Methods

Patients were questioned with regard to symptoms of urinary frequency, urethral discharge, suprapubic, perineal or scrotal pain, and joint or lower back pain. They were asked to assess their symptoms as mild, moderate or severe. A similar assessment was made during follow-up and the patient's impression of the effect of treatment assessed as unchanged, improved or cured.

Serum biochemistry included ESR, differential white cell count and c-reactive protein (CRP, negative values <10 mg/l). Microscopy of the EPS was performed at a magnification of ×400. A leucocytosis of 20 WBC/high power field or clumping of cells was considered pathological.

Antibodies against *Escherichia coli* and *Proteus mirabilis* (Jodal *et al.*, 1975; Larsson *et al.*, 1988) and against *Chlamydia* and *Mycoplasma hominis* were titrated. During the 12-week course of treatment, patients were followed up at 5 to 6 weeks; they were seen again 1 week, 5 to 6 weeks, 3 months and 6 months after completing treatment.

Bacteriological methods

The EPS and urine samples were stored immediately after collection at 4°C and cultured in various dilutions on blood agar and McLeod plates within 1 h. Preliminary studies revealed no difference in the number of bacteria or type of isolates between cultivations done within 5 min of sampling and those done at 1 h. The same technician was employed throughout the study. Patients had abstained from ejaculation for at least 3 days before the samples were collected.

Results

Of the 122 patients, 43% had Gram-positive and 13% Gram-negative organisms in sufficient numbers for the diagnosis of chronic bacterial prostatitis (Table 1). Of the 16 control patients, 12 had Gram-positive organisms on culture localised to the prostate. None of the controls had Gram-negative organisms. *Staph. epidermidis* was the most common Gram-positive followed by various strains of streptococci, while *E. coli* was the dominant Gram-negative organism, followed by *Klebsiella pneumoniae* and *Proteus* spp. The latter was second to *E. coli* as a potential pathogen for prostatitis (Tables 2 and 3).

Table 1 Patients and Controls with Prostatitis caused by Gram-positive (G+) or Gram-negative (G−) Bacteria

Patients (n=122)		*Controls (n=16)*	
G+	*G−*	*G+*	*G−*
52 (43%)	16 (13%)	16 (75%)	0

Table 2 Species of Gram-positive Bacteria found in Patients and Controls

Species	*Patients (122)*	*Controls (16)*
Staph. epidermidis	31	6
Staph. hominis	1	
Staph. haemolyticus	2	
α-streptococci	5	2
Str. group B	4	1
Str. group D	4	2
Micrococcus luteus	1	1
Gram-pos. rods	4	
Total	52 (43%)	12 (75%)

Table 3 Species of Gram-negative Bacteria isolated from Patients

	Localisation of bacteria	
Species	*Any level*	*Prostatitis*
E. coli	9	9
Klebsiella spp.	5	1
Proteus spp.	4	3
Enterobacter spp.	3	2
Pseudomonas spp.	3	2
Branhamella catarrhalis	2	2
Serratia spp.	1	1
Citrobacter spp.	1	
Acinetobacter spp.	1	
Other gram-neg. rods	4	2
Total	33 (28 patients)	22 (16 patients)

None of the patients had positive cultures for *Chlamydia*, although 6 had serum titres from 1/8 to 1/64 that were above normal ($<\frac{1}{8}$). All patients had normal titres against *Mycoplasma*. Serum antibodies against *E. coli* and *Proteus* gave no valuable information in this study.

Results in 33 patients studied separately after treatment with either cefadroxil or co-trimoxazole

The symptoms in these patients varied widely but the results are summarised in Table 4. Four patients stopped treatment as a result of side effects (mild diarrhoea in 3 patients on cefadroxil and a rash in 1 patient on co-trimoxazole). One patient was excluded 1 month after completing treatment because another antibiotic was administered for an exacerbation of his prostatitis. One-quarter of the patients were symptom-free after 6 weeks of treatment and about half by the end of the course. In a third of the patients the symptoms were unchanged 6 months after finishing treatment. There was no statistical difference in response between the two groups. The bacteriological changes after treatment are shown in Table 5. Bacteria present in significant amounts within the first month after treatment are labelled as new isolates of Gram-positive or Gram-negative when species other than the original one were present. The organism present initially was eliminated in about half of the patients by the end of the 12-week course of treatment. However, 25 of the 29 patients still had significant bacterial growths on culture within 1 month after treatment.

Of the 26 patients with Gram-positive organisms 5 relapsed; 1 of these resolved spontaneously but 4 remained infected at 26 weeks. In 13 patients a new Gram-positive organism was isolated; 12 resolved spontaneously but 1 remained infected at 26 weeks. Gram-negative organisms appeared in 5/26 patients; 2 of these resolved spontaneously and 3 remained infected at 26 weeks.

Treatment eradicated infection in the 3 patients with initial Gram-negative bacteria in the EPS, but 1 month after treatment 1 patient developed a Gram-positive and 1 a Gram-negative infection. Both of these resolved spontaneously.

Relationship between clinical and bacteriological findings

There was no difference in symptoms between the patients with Gram-negative and those with Gram-positive infections. Relief of symptoms was related to elimination of bacteria: of the 14 patients relieved of symptoms only 1 had a significant bacterial infection at 6 months, but 7 of 10 patients in whom symptoms remained unchanged had a significant bacterial infection ($P < 0.01$).

The mean value of the pH of the EPS was 7.8 ± 0.39 (SD) before treatment; after treatment it was 7.1 ± 0.44 (same level as in the controls (7.1 ± 0.41)). The decrease in pH did not differ between patients with relief of symptoms and those without. The leucocyte count of the EPS was >20/field (×400) in all patients before treatment and correlated with symptomatic improvement after treatment. Thus in 12 of 13 patients without symptoms the count was <10 and 15 in 1, but <10 in only 2 of 8 patients in whom symptoms were unchanged.

Discussion

In this study, Gram-negative organisms were isolated in a minority of patients (13%) with chronic prostatitis. This is in agreement with previous reports (Drach, 1974; Mårdh and Colleen, 1975). The pathogenic role of Gram-positive bacteria is controversial, since cultures at different times may show different species of Gram-positives in signifi-

Table 4 Results of Treatment

		During treatment	*After treatment*			
Drug	*Effect*	*6 weeks*	*1 week*	*1 month*	*3 months*	*6 months*
Cefadroxil (n = 15)	Cured	4	10	9	9	9
	Improved	9	3	3	4	1
	Unchanged	2	2	3	2	5
Stopped drug		1				
Co-trimoxazole (n = 14)	Cured	2	5	6	5	5
	Improved	8	8	3	5	4
	Unchanged	4	1	5	4	5
Stopped drug		3				

Table 5 Bacteriological Findings after Treatment (Number of patients)

Before treatment		*After treatment*					
		1–4 weeks				*12–26 weeks*	*26 weeks*
Bacterial organism	*Pat no.*	*Cured*	*Relapse*	*New isolates of G+*	*G−*	*Resolved spontaneously*	*Infected*
Gram-pos.	1	3					
	2						
	3						
	4		5			1	4
	5						
	6						
	7						
	8						
	9			13		12	1
	10						
	11						
	12						
	13						
	14						
	15						
	16						
	17						
	18						
	19						
	20						
	21						
	22				5	2	3
	23						
	24						
	25						
	26						
Gram-neg.	27	1					
	28			1		1	0
	29				1	1	0

cant numbers (Fowler and Mariano, 1984). The clinical response to a 12-week course of antibiotics, with relief of symptoms in practically all patients with Gram-positive infection, supports the argument that Gram-positives are putative pathogens in bacterial prostatitis.

It has been shown that some strains of *Staph. epidermidis* cause an antibody response in experimental infections (West *et al.*, 1983). We have also been able to demonstrate an individual immune response of *Staph. epidermidis* isolated from the EPS of patients with prostatitis (Wedrén *et al.*, 1987).

In only 3/26 patients with Gram-positive infection were bacteria eliminated for the duration of the study with the initial treatment. However, in 12/13 patients reinfected with a new strain spontaneous resolution occurred. By contrast, only 1/5 patients with reinfection with the same organism resolved spontaneously.

The other 4 patients with bacterial prostatitis after 6 months' follow-up may well have been infected with a more virulent *Staph. epidermidis* strain than the 13 reinfected with a new strain. It seems that if the recolonisation is caused by commensals, these bacteria may protect the host from being reinfected by a more virulent Gram-positive or Gram-negative strain. Similar findings in other ecological situations indicate that the normal flora of the mucous membranes constitute an important barrier against invading micro-organisms. Thus colonisation with one strain of *Staphylococcus aureus* can hinder colonisation with another strain of the same species (Shinefield *et al.*, 1975). Furthermore, Martin and White (1968) demonstrated that coagulase-negative staphylococci as well as "diphtheroids" prevented colonisation by more virulent staphylococci. Convincing clinical evidence of the protective capacity of the normal flora has also been presented by Sanders

(1975) and Sanders *et al.* (1977), who demonstrated that α-streptococci normally present in the throat flora protected against group A streptococcal infections, while Sprunt *et al.* (1971) and Sanders *et al.* (1976) showed that eradication of the α-streptococci by excessive antibiotic treatment resulted in overgrowth of Gram-negative bacteria in the throat.

Our findings that 5 patients with Gram-positive bacteria at the start of treatment were reinfected with Gram-negatives 1 to 4 weeks after the end of antibiotic treatment might be another reflection of bacterial interference. Three of these patients were still colonised at follow-up 6 months later. We support the assumption that bacterial prostatitis may be caused by aggressive strains of Gram-positive organisms capable of disturbing the ecological balance of bacterial flora in the urethra. It is also possible that antibiotic treatment may contribute to this phenomenon and in some cases contribute to a Gram-negative urethral colonisation.

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Comparative Histopathology, Microradiography and Per-rectal Ultrasonography of the Prostate using Cadaver Specimens

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Summary—A technique for examining cadaver prostates by per-rectal ultrasonography has been developed. The ultrasonic plane was defined and corresponding sections taken for microradiographic and histopathological examination. The technique has enabled a comparison to be made of the structural changes that occur in the prostate in disease states and the corresponding ultrasonic features.

The representation of prostatic diseases by per-rectal ultrasonography and its mechanism is controversial. Early reports suggested that cancer was represented by focally dense asymmetrical areas (Resnick *et al.*, 1978) and many workers have described cancer as being hyperechoic on ultrasound scanning (Watanabe *et al.*, 1975; Harada *et al.*, 1980; Rifkin *et al.*, 1983). However, Lee *et al.* (1985) described cancer as being represented by low echoes. They noted that all carcinomas were less echogenic than the normal prostate and that they all originated in the peripheral zone.

Correlation of ultrasound scans with the histopathology of whole prostates has been suggested as a means of understanding the representation of different disease processes of the prostate gland (Rifkin *et al.*, 1986). Various mechanisms of production of different types of echo have been suggested. Greenberg *et al.* (1981) considered that cancers may have surrounding high echoes due to increased collagen. However, the mechanism by which different echo patterns are produced is not understood. Correlation with the structure of the prostate gland in both normal and diseased states would provide useful information and is now possible using microradiography (Davies *et al.*, 1988). Radiography of the prostate gland has enabled investigation of its calcification (Gibbs *et al.*, 1975) but tissue definition has been poor. The development of microfocal X-ray units has enabled specimens to be radiographed with minimal blurring of the image and a technique of projection X-ray microscopy has been developed by Davies (1986). Tissue freeze drying, together with the use of microfocal units, has enabled the development of a technique for radiography of the prostate, producing detail of the structure and calcification (Davies *et al.*, 1988). The aim of this study was to develop a technique that enabled a correlation to be made of the histopathology, microradiography and ultrasonography of cadaver prostates. The structure and corresponding ultrasound echogenicity of the prostate in normal and disease states can then be examined.

Materials and Methods

The prostate, bladder, rectum and anus were removed *en bloc* transabdominally (Fig. 1) and washed, after having obtained legal and ethical permission. The specimens were placed in physiological saline and scanned as soon as possible.

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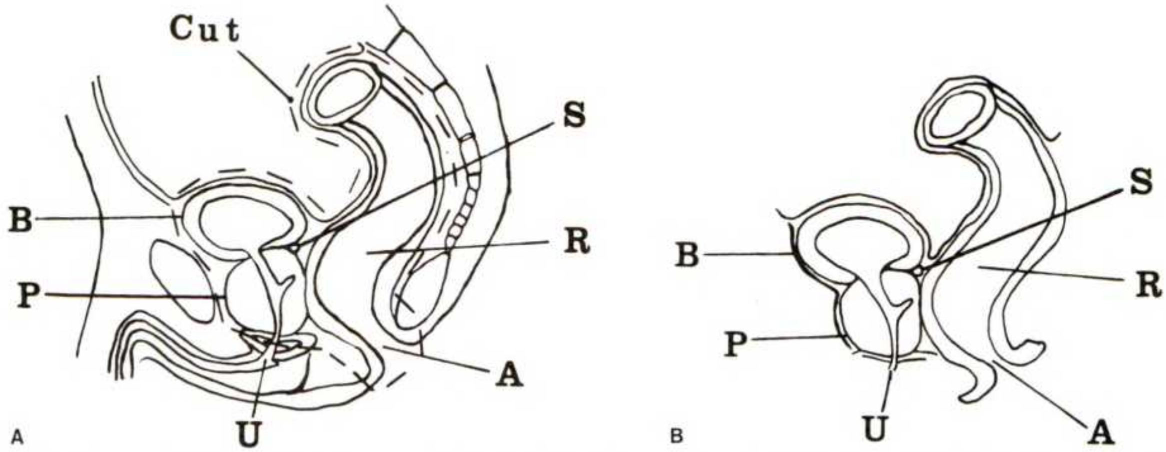

Fig. 1 Prostate, bladder, rectum and anus. (A) Pelvis. (B) Specimen. B = Bladder, P = Prostate, U = Urethra, A = Anus, R = Rectum, S = Seminal vesicles, Cut = Dissection of specimen.

Deterioration in the quality of scanning is inevitable from the time of death. However, all samples were scanned within 48 h, during which time the quality remained good.

A specially designed perspex tank was constructed which allowed the specimen to be suspended in saline and scanned transrectally (Fig. 2). Consistent orientation of the prostate was maintained for standardisation. The prostates were scanned downwards at 5-mm intervals and the precise level of each scan determined.

The prostate was scanned by a transrectal radial scanner (3.5 MHz) (model ASU-8R-C) mounted on an Aloka chair (model SSD-501). Processing and recording were carried out using a Searle Pho/Sonic Alpha Series Ultrasound Scanner which provided permanent X-ray film recordings.

After scanning, the glands were dissected from the rest of the cadaver specimen and fixed in buffered formol saline for 3 days. They were then accurately suspended, using 2 needles, in a specially designed box and embedded in gelatin. Once the gelatin had solidified the box was dismantled, thus enabling the prostate gland to be accurately sectioned; 1-mm sections were obtained for microradiography and 4-mm sections for histopathological study (from which 5-μ sections were cut at appropriate levels). This resulted in a range of 3 to 12 histopathological sections, microradiographs and ultrasound scans per case.

Histopathology

Complete transverse 5-μ sections were cut and stained with haematoxylin and eosin. The quality of the histopathology slides was seen to be compatible with other post mortem preparations. The

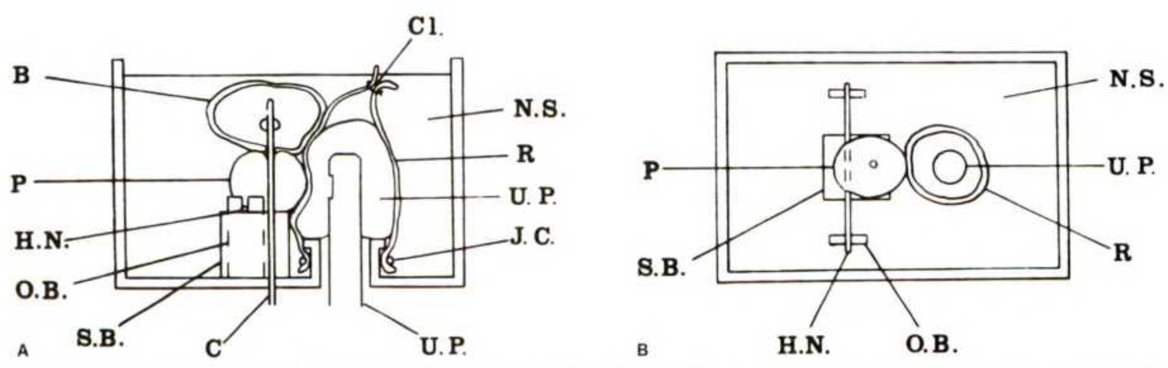

Fig. 2 Scanning tank. (A) Horizontal view. (B) Plan view. B = Bladder, P = Prostate, R = Rectum, H.N. = Horizontal needle, O.B. = Orientation block, S.B. = Support block, C = Catheter, U.P. = Ultrasound probe, J.C. = Jubillee clip, N.S. = Normal saline, Cl. = Clip, U.B. = Ultrasound balloon.

histopathological features recorded included muscle, fibrous and adipose tissue, benign glandular elements, stromal nodules and carcinoma. Grading of the cancers was not attempted because of the loss of some architectural and cytological detail. However, diagnosis of the presence or absence of malignant disease was possible in most cases, with only occasional areas being recorded as equivocal.

Microradiography

The 1-mm sections for microradiography were initially freeze dried. This is essential to produce microradiographs which reveal structural detail as well as calcification. The sections were placed between metal grids to prevent warping. Microradiographs were obtained using an X-ray microscope (operating range 7–30 Kev) using 15 Kev for this investigation (Davies *et al.*, 1988). The results were recorded on N.D.T.45 Dupont film.

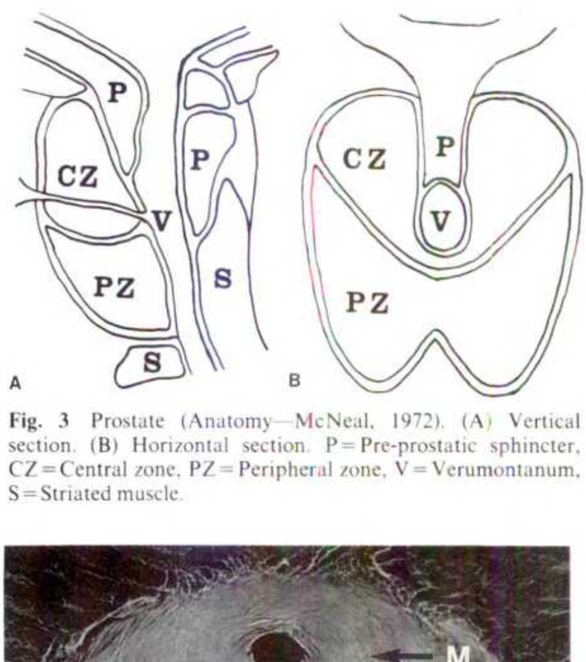

Fig. 3 Prostate (Anatomy—McNeal, 1972). (A) Vertical section. (B) Horizontal section. P = Pre-prostatic sphincter, CZ = Central zone, PZ = Peripheral zone, V = Verumontanum, S = Striated muscle.

Comparative analysis

Each ultrasound scan had a corresponding microradiograph and histopathological slide. To allow comparison of corresponding areas, each investigation was divided by a 4 × 4 grid, producing 16 areas per section. Histopathological, microradiographic and ultrasonic findings were recorded within all the 16 individual squares.

Results

A total of 100 cadaver prostates was examined; 29 were malignant and 71 benign. Ages ranged from 17 to 90 years (mean 63). Histopathological slides of normal glands were reviewed with their structure as shown by the microradiographs and the resulting ultrasound echo patterns.

The normal gland

Pre-prostatic sphincter. The upper sections showed hypo-echoeic periurethral areas which correlated with periurethral muscle on histopathology. Microradiographs of these areas (Fig. 4A) showed amorphous or finely regular structure corresponding with the hypo-echoeic echoes (Fig. 4B). This muscle is the pre-prostatic sphincter as described by McNeal (1972) (Fig. 3).

Central zone. The central zone has a reticular structure similar to (but coarser than) the peripheral zone (Fig. 4A). It produces mid-range echoes on

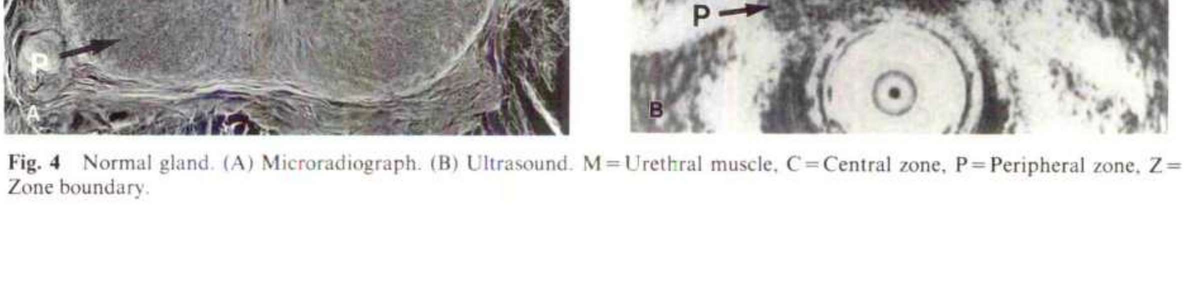

Fig. 4 Normal gland. (A) Microradiograph. (B) Ultrasound. M = Urethral muscle, C = Central zone, P = Peripheral zone, Z = Zone boundary.

ultrasonography and forms the base of the gland (Fig. 4B).

Peripheral zone. The normal peripheral zone consists of benign glands and is located at the apex of the prostate. The structure is seen to be of a fine reticular nature (Fig. 4A), producing mid-range echoes on ultrasonography (Fig. 4B) which can be differentiated from the central zone.

Muscle/gland boundary. Normally, a distinct boundary exists between the hypoechoic urethral muscle, which has an amorphous structure on microradiography, and the mid-range echoes of the rest of the gland, which has a fine reticular structure on microradiography (Figs 4A and 4B).

Discussion

The technique of comparative histopathology, microradiography and per-rectal ultrasonography of cadaver prostates has been developed and allows the structure and resulting echogenicity of the prostate gland to be examined.

The normal gland contains periurethral muscle which has an amorphous structure giving rise to low ultrasonic echoes. The rest of the gland consists of glandular tissue which has a reticular structure giving mid-range echoes on ultrasonography.

The echogenicity of the prostate gland on ultrasonography is therefore related to is internal structure and this has been demonstrated in the normal gland. This technique may be used to study the structure and echogenicity of the prostate gland in both normal and diseased states.

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High Dose Polyoestradiol Phosphate with and without Acetosalicylic Acid versus Orchiectomy in the Treatment of Prostatic Cancer

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Summary—The clinical efficacy of high dose (160 mg) polyoestradiol phosphate (PEP) was compared with that of orchiectomy in a prospective randomised multicentre study including 200 prostatic cancer patients. The effect of daily low dose (75 mg) acetosalicylic acid (ASA) on possible cardiovascular complications during the first 6 months of therapy was also evaluated.

Oestrogen-treated patients had more progressions, but follow-up was too short to draw any definite conclusions on the efficacy of treatment. There was no cardiovascular mortality and there were no thromboembolic complications in any treatment group. It was concluded that parenteral high dose PEP is not associated with an increased risk of cardiovascular complications and there is no need for daily low dose ASA.

Orchiectomy and oestrogens have been the most widely used treatments for prostatic carcinoma for nearly 50 years. Oestrogen is claimed to be as effective as orchiectomy in terms of its inhibitory effect on cancer, but it is associated with an increased risk of cardiovascular complications (Blackard *et al.*, 1970; Hedlund *et al.*, 1980; Glashan and Robinson, 1981; Haapiainen *et al.*, 1986). The mechanism underlying these complications is not yet fully understood. The adverse effects are partly dose-dependent (Bailar *et al.*, 1970) and may be explained by changes in plasma lipoproteins, coagulation factors and fibrinolysis (Glashan and Robinson, 1981; Henny *et al.*, 1984; Rösner *et al.*, 1985; Henriksson *et al.*, 1986).

The purpose of the present randomised study was to compare the clinical efficacy of polyoestradiol phosphate with that of orchiectomy and to evaluate the effect of daily low dose acetosalicylic acid on possible cardiovascular complications during the first 6 months of oestrogen therapy, when the incidence of these complications is highest.

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Patients and Methods

The study group comprised 200 patients with histologically and/or cytologically verified prostatic carcinoma diagnosed between January 1985 and March 1987 in 9 Finnish hospitals. The exclusion criteria were: previously diagnosed and treated prostatic cancer, history of acute thromboembolic episode, non-respondent decompensated cardiac insufficiency, known severe liver disease, daily use of ASA, allergy to ASA and anticoagulant therapy.

The patients were randomly allocated to 3 treatment groups. A box of envelopes was delivered to each hospital, with one-third of the envelopes coded for each treatment arm. Enrolment was stopped when 200 eligible patients had been included. The orchiectomy group consisted of 75 patients (mean age 72.4 years, range 56–84). Bilateral orchiectomy was either total or subcapsular. A group of 125 oestrogen-treated patients were randomised to receive in a double-blind design either ASA (71 patients, mean age 69.0 years, range 52–84) or placebo (54 patients, mean age 70.8 years, range 55–82). Oestrogen therapy consisted of intramuscular polyoestradiol phosphate (Estradurin) 160 mg/month. Oral ASA (75 mg) or placebo was given daily during the first 6 months of oestrogen therapy. Three patients in the orchiectomy group were later withdrawn, 6 in the PEP+ASA group and 8 in the PEP+placebo group. The causes of withdrawal were: use of ASA after onset of therapy, interruption in oestrogen administration and loss to follow-up.

At the time of diagnosis there were no significant differences between the groups in terms of local extent of tumour, grade of malignancy and presence of distant metastases (UICC, 1982) (Table).

The patients were examined after undergoing treatment for 3 and 6 months. Progression of disease was evaluated according to the SPCG criteria (Scandinavian Prostatic Cancer Group), a modification of the EORTC criteria (Schroeder, 1984). Progression was defined as an increase in prostatic tumour size of more than 25% and/or an increase in the size of metastases of more than 25%, or the appearance of a new metastasis. Progression was not based on changes in prostatic acid phosphatase or performance status only. Possible cardiovascular complications included myocardial infarction, cerebrovascular complications, pulmonary embolism and deep vein thrombosis. This report is an analysis of the first 6 months of follow-up of all patients.

Results

One of 75 orchiectomised patients and 12 of 125 oestrogen-treated patients showed progression of disease; 3 patients in the orchiectomy and 2 in the oestrogen group died of prostatic cancer before the progression was recorded on the follow-up examination, which in practice means progression. There was no cardiovascular mortality and there were no thromboembolic complications in any group. No allergic reactions or haemorrhagic complications were seen in patients receiving ASA.

Discussion

In the present study the efficacy of high dose polyoestradiol phosphate was compared with that of orchiectomy. The effect of daily low dose acetosalicylic acid on possible cardiovascular complications during the first 6 months of therapy was also evaluated. The oestrogen-treated patients exhibited more progressions during the first 6 months than those who had undergone orchiectomy. However, because of the short follow-up no definite conclusions can be drawn on the progression and mortality rates of the two treatment arms. Our previous investigation (Finnprostate I) showed significantly more progressions during the first 2 years in the orchiectomy than in the oestrogen group when polyoestradiol phosphate was combined with ethinyloestradiol (Haapiainen *et al.*, 1986).

In Finland, orchiectomy has traditionally been the treatment of choice. Polyoestradiol phosphate has been the second most common treatment and in combination with a potent gonadotrophin inhibitor, ethinyloestradiol, it was introduced in the treatment of prostatic cancer in Sweden in 1971 (Jönsson, 1971). A lower dose (80 mg) of polyoestradiol phosphate in combination with ethinyloestradiol was used in the Finnprostate I study (Haapiainen *et al.*, 1985), where 19 of 146 oestrogen-treated patients (13%) had thromboembolic or other cardiovascular complications during the first 6 months. This is in accordance with the results of other studies; the incidence of cardiovascular complications is highest during the first few months of oestrogen therapy (Byar, 1973; Hedlund *et al.*, 1980; Glashan and Robinson, 1981; Haapiainen *et al.*, 1986; de Voogt *et al.*, 1986).

In the present study, daily low dose ASA was combined with oestrogen therapy during the most vulnerable period of the first 6 months. During the past years the benefit of daily ASA has been well documented as a preventive factor in cerebral and coronary thrombosis (Cairns *et al.*, 1985; Grotta, 1987). The optimal dose of ASA is still unknown and the relationship between the antiplatelet effects of ASA and its antithrombotic efficacy has not been

Table Extent of Primary Tumour (T classification), Presence of Distant Metastases (M classification) and Differentiation Grade (G classification) in Patients with Prostatic Cancer according to Treatment Groups

Treatment	*No. of patients*	*T0–2*		*T3–4*		*M0*		*M1*		*G1*		*G2*		*G3*	
		N	*(%)*	*N*	*(%)*	*N*	*(%)*	*N*	*(%)*	*N*	*(%)*	*N*	*(%)*	*N*	*(%)*
Orchiectomy	75	7	(9)	68	(91)	47	(63)	28	(37)	15	(20)	45	(60)	15	(20)
PEP+ASA	71	3	(4)	68	(96)	32	(45)	39	(55)	18	(25)	45	(63)	8	(11)
PEP+placebo	54	2	(4)	52	(96)	34	(63)	20	(37)	12	(22)	37	(69)	5	(9)

clarified; doses as low as 40 mg/day may be as effective as larger doses (Wecksler *et al.*, 1985; Grotta, 1987). The dose used in the present study was 75 mg/day. Its anti-thrombotic efficacy could not be established because there were no thrombotic complications in any group. This low dose ASA was not associated with haemorrhagic complications.

The most interesting finding in the present study was that intramuscular polyoestradiol phosphate is not associated with an increased risk of thromboembolic or other cardiovascular complications. During the first 6 months, none of the 125 oestrogen-treated patients (with or without ASA) had any such problems. This emphasises the importance of excluding all patients with a history of thromboembolic episodes. A previous history of cardiovascular disease should be considered when choosing between orchiectomy and oestrogens.

In an earlier study, the combination of a lower dose (80 mg) of intramuscular polyoestradiol phosphate and oral ethinyloestradiol was associated with a number of cardiovascular side effects during the first few months of oestrogen therapy (Haapiainen *et al.*, 1985). It seems possible that bypassing the portal circulation, for instance by parenteral administration, might be beneficial with respect to liver-related side effects following oral oestrogen (Stege *et al.*, 1987).

It may be concluded that high dose polyoestradiol phosphate is not associated with an increased risk of cardiovascular complications. Therefore there is no need for daily low dose ASA in patients treated by intramuscular polyoestradiol phosphate 160 mg/month. Although minor differences were observed in the clinical efficacy of orchiectomy and high dose polyoestradiol phosphate, the follow-up was too short to draw any definite conclusions.

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Neurophysiological Assessment of the Central Motor Pathway to the External Urethral Sphincter in Man

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Summary—A recently developed neurophysiological method by which the motor cortex in man can be electrically stimulated has been applied to the assessment of the central motor pathway to the external urethral sphincter. It was observed that there was parallel activation of the anal sphincter, the pelvic floor and the lower limb muscles, voluntary facilitation and marked inhibition during micturition.

This method can be used to assess the volitional and the various segmental and suprasegmental influences on the behaviour of the external urethral sphincter. Unfortunately, the poor tolerance of subjects to the scalp sensations caused by the electrical stimulus is a major limitation to its clinical use, though this should be obviated by the introduction of a cortical magnetic stimulator.

In 1980 Merton and Morton succeeded for the first time in evoking contractions of limb muscles by transcranial electrical stimulation of the motor cortex in man. When applied to the skin overlying the cervical and lumbar spinal cord, the stimulator they devised could also evoke action potentials in the anterior spinal roots. They were able to record short latency, well synchronised muscle action potentials from the external anal sphincter following lumbar and cortical stimulation. They also discovered that a peculiar property of the muscular response evoked by cortical stimuli was a considerable lowering of excitability thresholds during sustained voluntary contractions of the recorded muscles. This facilitatory effect did not occur with spinal stimuli (Merton *et al.*, 1982). Swash and Snooks (1986) reported the application of this new technique to the assessment of the lower motor neurone control of the pelvic floor muscles and the external anal sphincter.

The aim of the present study was to establish whether the new technique could be used to assess the cortical motor pathway control of the external urethral sphincter.

Patients and Methods

The study was restricted to 40 patients (13 men and 27 women) with disorders of continence requiring urodynamic investigation, to which cortical stimulation was added. Four patients were neurologically normal; the other 36 had suffered a cerebrovascular accident causing hemiplegia. Their ages ranged from 22 to 82 years.

A special stimulator (Cortical Stimulator D180; Digitimer Ltd) based on the design of Merton and Morton (1980) was used to stimulate the central motor pathway transcranially. A 750 V capacitive discharge, exponentially decaying with a time constant of 100 μs, was applied to the scalp through metallic circular electrodes (20 mm diameter) wrapped in gauze and soaked in physiological saline. The electrodes were mounted on separate wooden handles and firmly pressed on to the vertex (anode) and immediately below the frontal hairline in the midline (cathode).

Conventional EMG equipment (Medelec MS 92) was used to record the evoked muscular activity sampled by bipolar needle electrodes (with the cannula grounded) inserted into the periurethral sphincter. These were inserted laterally at 3 o'clock in women and by the perineal route in men, aiming

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at the prostatic apex. A second channel was used to record from the external anal sphincter. The final electrode positions and gain settings were achieved by visual and acoustic monitoring of spontaneous EMG activity. A band-pass filter (6 dB/octave) between 20 and 3000 Hz was used.

Patients were stimulated in the following states:

(1) Under baseline conditions with the bladder empty and the patient relaxed.
(2) During voluntary sustained perineal contraction with the bladder empty.
(3) During normal micturition.
(4) After completion of micturition, to check that the electrodes had retained their position throughout the procedure.

When the tolerance of the subject for the procedure was good, responses to at least 2 successive scalp stimuli were recorded for each of the 4 states in order to assess the reproducibility of responses.

Results

Under baseline conditions

Cortical stimulation evoked bursts of EMG which lasted up to 40 ms. This was obtained from both sphincters in all subjects (Fig. 1). Under baseline conditions, the latency period of these responses varied from 18 to 39.3 ms (mean 30.93) for the urethral sphincter and from 18 to 46.8 ms (mean 34.54) for the anal sphincter.

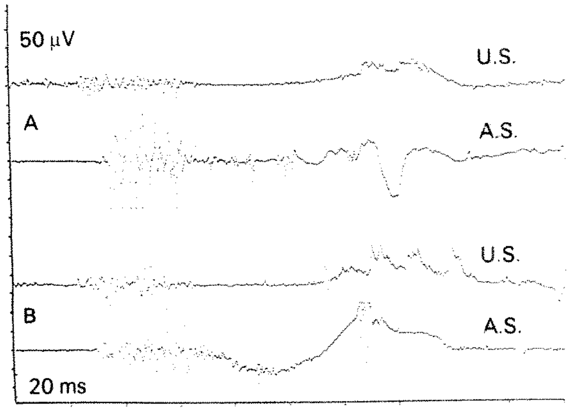

Fig. 1 EMG bursts evoked in urethral (U.S.) and anal (A.S.) sphincters by two successive (A and B) vertex stimuli under baseline conditions. Horizontal calibration 20 ms; vertical calibration 50 μV.

Table Intra-subject Urethral Sphinter Test-retest Latency to Repeated Stimulation under Baseline Conditions (in ms)

Subject		*Stim. 1*	*Stim. 2*	*Stim. 3*	*Stim. 4*
1	U.S.	34	30	32.8	—
	A.S.	30	30.8	26.4	—
2	U.S.	27.6	33.6	33.6	30.2
	A.S.	36	43	43.8	38.8
3	U.S.	33	31.6	29	—
	A.S.	28.6	31.6	31.6	—
4	U.S.	30.8	35.4	38.4	—
	A.S.	44	45.6	46.8	—
5	U.S.	35.6	35	—	—
	A.S.	44	35	—	—
6	U.S.	22.2	22.2	—	—
	A.S.	34.4	34.4	—	—
7	U.S.	29	30.6	30.6	—
	A.S.	33.2	39.4	41.8	—
8	U.S.	30	30	38	—
	A.S.	45	36	46	—
9	U.S.	18	23	23	23
	A.S.	18	30	30	30
10	U.S.	26.6	27.6	28	—
	A.S.	44	48	46	—
11	U.S.	33.8	32.4	34.8	33.8
	A.S.	32.4	40	38.2	40
12	U.S.	27	27.6	—	—
	A.S.	27.6	27.6	—	—
13	U.S.	28.8	32.2	30.8	30.8
	A.S.	36	38.8	38.4	38.8
14	U.S.	31	31	—	—
	A.S.	28	28	—	—
15	U.S.	32.1	39.3	39.3	—
	A.S.	32.1	37.5	44.5	—
16	U.S.	27.8	27.8	28.1	27.8
	A.S.	—	—	—	—

U.S. Urethral sphincter.
A.S. Anal sphincter.

Serial measurements under baseline conditions were performed in 16 subjects. Intra-session test-retest latency variation is shown in the Table, where it can be seen that latency measurements were far from stable, more often showing a range than a single value. Sometimes, however, when the spontaneous tonic background activity was low and the patient fully relaxed, repeated stimulation yielded highly consistent latency values (Fig. 2).

During voluntary pelvic floor muscular contraction with the bladder empty

An effect of sustained pelvic floor muscular contraction was an increase in response amplitude or motor unit recruitment pattern or both. The most conspicuous effect of voluntary activation with cortical stimulation was a latency decrease of several ms

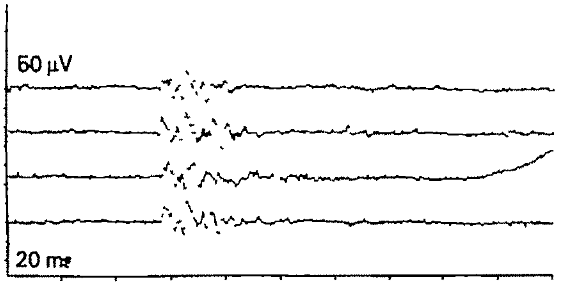

Fig. 2 Highly stable urethral sphincter responses to 4 repetitive stimuli in a well relaxed subject (No 16 in Table) Horizontal calibration 20 ms; vertical calibration 50 μV.

(Fig. 3). This was almost always unmistakable despite frequent blurring of the exact latency value due to enhanced background activity. Such latency decreases and amplitude enhancements during voluntary sustained contraction have been documented for limb muscles (Rothwell *et al.*, 1987). To illustrate this effect, recordings were also made from the authors' hand muscles. Figure 4 depicts surface recorded evoked EMG responses from the left thenar eminence to a fixed scalp shock. A definite latency reduction, from 24.2 ms when the recorded muscles were totally relaxed to 18.1 ms under maximal background voluntary contraction, was noted, together with an amplitude increase of up to 400%.

During mid-stream micturition

During micturition, a clear-cut inhibition of the evoked response took place in both sphincters. Considerable latency increases (to more than double the baseline value) or even complete EMG silence could be seen during the maximal voiding flow (Fig. 5).

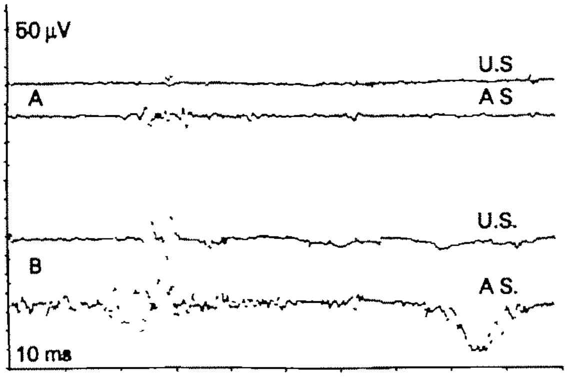

Fig. 3 Facilitation effect: responses from both sphincters under (A) baseline conditions: U.S. latency 30 ms, A.S. latency 27 ms, and (B) voluntary pelvic floor contraction: U.S. latency 21 ms, A.S. latency 18 ms An increase in motor unit action potentials density and overall response amplitude accompany the latency reductions. Note blurring of exact onset latency value due to enhanced background activity for the anal sphincter. Horizontal calibration 10 ms; vertical calibration 50 μV.

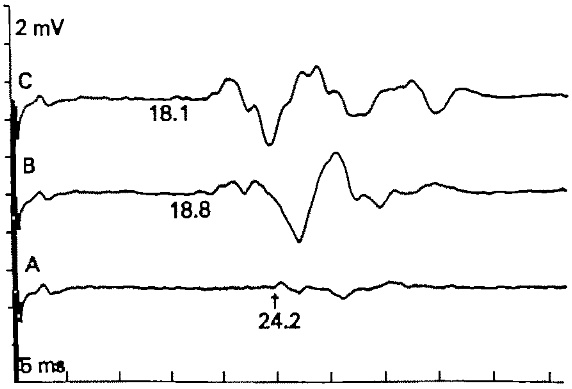

Fig. 4 Facilitation effect in thenar muscles: responses to the same cortical shock under 3 conditions. (A) Hand fully relaxed: onset latency 24.2 ms (B) Slight contraction: onset latency 18.8 ms. (C) Strong contraction: onset latency 18.1 ms. Horizontal calibration 5 ms, vertical calibration 2 mV.

After micturition

As a check that the changes observed under conditions (2) and (3) were not due to electrode displacement, responses were obtained again after completion of micturition when the patient was fully relaxed. Responses similar to those obtained under baseline conditions were again observed (see lower part of Fig. 5). In 2 patients the electrodes had been dislodged during voiding.

Discussion

The results demonstrate the presence of evoked EMG bursts in the external urethral sphincter of human subjects to transcranial motor cortex stimulation. Although problems remain, several properties of the response revealed in the present study pave the way for some interesting physiopathological applications.

The method is technically easy to apply in both sexes, but high voltage stimuli applied to the scalp are unpleasant, especially when repeated several times. For this reason, only maximal (750 V and 100 μs time constant decay) shocks were applied, without investigating different stimulus parameters. This kept the number of scalp stimuli to a minimum.

Vertex stimuli evoke EMG bursts in both anal and urethral sphincters, as well as in the pelvic floor and the lower limb muscles. This widespread activation may cause some confusion when record-

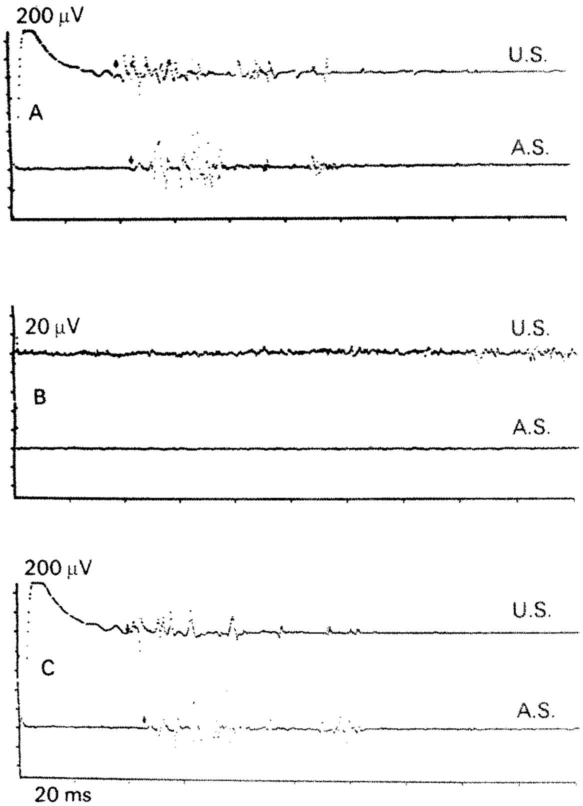

Fig. 5 Sphincter refractoriness during voiding. (A) Responses under baseline conditions in both sphincters. (B) Absence of evoked and spontaneous activity during voiding. (C) Baseline condition responses after bladder emptying. Horizontal calibration 20 ms; note vertical calibration changes: amplifiers' gain is greater in (B) than in (A) and (C).

ing from small sphincters embedded within powerful muscles that also contract: hence the need for a recording technique (*i.e.* a bifilar needle electrode) which allows precise muscle sampling. Once this has been done, the variety of the muscles activated by the cortical stimulus is probably a definite advantage, since multiple simultaneous recordings could allow comparison between discrete portions of the efferent motor pathway. How the motor pathways subserving urethral and anal sphincters compare with those controlling skeletal muscles can now be estimated in both health and disease.

The latencies of the evoked EMG bursts exhibited wide-ranging inter- and intra-individual variations. Part of the inter-individual differences is probably due to the heterogeneity of the population studied in terms of age, gender, body size, urological and neurological status.

The important intra-individual latency fluctuations of the sphincter responses observed in this study constitute a challenge and seem to consist of 2 main parts. The first is a kind of intrinsic variability which is difficult to control and which contributes to the high test-retest latency fluctuation under baseline relaxed conditions (Table), although good relaxation by the subject probably lessens this variability. The second is a latency modulation, linked with facilitation during voluntary pelvic floor contraction and inhibition during voiding.

It must be added that some degree of imprecision in latency measurements is directly correlated to the level of background EMG activity. Had multiple stimuli been better tolerated, this could have been overcome by averaging several responses in order to increase the signal to noise ratio. This generally poor latency stability precludes the reliable use of the method to measure a central motor tract conduction velocity such as calculated for limb muscles by Hess *et al.* (1986). They subtracted the latencies of responses evoked by cortical and spinal stimuli.

A discussion of the physiological mechanisms underlying the latency reductions observed in sphincters and limb muscles during voluntary contraction is beyond the scope of the present report (Day *et al.*, 1987). Current knowledge about this phenomenon suggests that a latency decrease may result from a rise in tonic background EMG activity, the latter not necessarily of volitional origin as demonstrated by tendon vibration experiments in limb muscles (Rossini, 1987). It is probable that the spontaneous latency fluctuations observed during repeated stimulation are partly due to fluctuations in sphincteric tone. The stable values observed in well relaxed subjects (Fig. 2) support this view.

Whatever the exact causes, it is expected that this phenomenon will provide a unique means of testing and quantifying the effects of volition on the urethral sphincter central motor pathway. On the other hand, the remarkable hypoexcitability of the sphincters demonstrated during micturition was somewhat unexpected. A transient urethral sphincter closure mimicking a voluntary interruption of micturition had been anticipated after stimulation of the central motor pathway to the periurethral striated muscle. Using the pudendal reflex arc, Dyro and Yalla (1986) showed that the external urethral sphincter becomes refractory to afferent pudendal stimulation during voiding. Because they observed that this refractory state during voiding was lost in patients with severe detrusor hyper-reflexia and unco-ordinated striated sphincter, they believe that the phenomenon is mediated by suprasegmental centres. The observation of a similar refractory state to electrically induced cortical descending volleys suggests that the central motor pathway itself could be inhibited by other central circuits. Alternatively, the central motor volley itself may be unchanged during voiding but nevertheless fails to depolarise the inhibited sphincter lower motor neurones above their firing threshold. The systematic study of patients with well documented lesions and various types of sphincter reactivity should help to clarify this matter.

With a combination of cortical, spinal, pudendal nerve stimulation and other reflex studies, the facilitation and inhibition effects created by voluntary background contraction and micturition respectively should provide the opportunity to test the system in a dynamic way, exploring the various suprasegmental and segmental excitatory and inhibitory influences involved in urethral and anal sphincter control.

The present line of study had to be discontinued because of the subjects' poor tolerance to scalp shocks, especially when repeated several times. The recent development (Barker *et al.*, 1985) of a magnetic device that induces the stimulating current within the brain without causing painful scalp sensations (Hess *et al.*, 1986) will help to increase its use in neuro-urological investigations.

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Histopathological Changes in Adult Cryptorchid Testes

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Summary—The histological specimens of 73 patients who presented with undescended testes after puberty were re-evaluated. None of the specimens revealed carcinoma *in situ* but in the specimens of 5 patients severe atypia was detected. None of the patients, including 5 with severe atypia, has shown any evidence of invasive testicular tumour during follow-up.

The propensity of an undescended testis to developing a germ cell carcinoma is widely recognised (Campbell, 1959; Krabbe *et al.*, 1979). It is crucial to predict the patients at risk as early as possible and it has been suggested that testicular biopsy may be useful in the early diagnosis of testicular tumours.

In this study we examined the incidence and significance or carcinoma *in situ* (CIS) and other histopathological lesions in patients with undescended testes who presented and were treated after puberty.

Patients and Methods

Histological material from 80 patients with undescended testes, biopsied between 1975 and 1987, were reviewed (A.A. and A.D.). Our treatment policy for this age group was to perform orchiectomy for unilateral cases and orchiopexy and biopsy for bilateral cases and those who refused orchiectomy. The histopathological specimens of 7 patients were insufficient for evaluation and the study group consisted of 90 orchiectomy specimens or testicular biopsies from 73 patients.

The cryptorchid testis was found in the inguinal area, high scrotum and abdomen in 74, 8 and 8 instances respectively. The age range at presentation was 15 to 46 years (median 22).

The biopsy specimens of 53 patients were fixed by immersion in buffered formalin solution and the remaining specimens of 20 patients were fixed in Bouin's solution. The light microscope slides were sectioned serially at 4 μm and stained with haematoxylin and eosin. The criteria for the diagnosis of CIS described by Skakkebaek *et al.* (1982) were used. The appearances may be summarised as "atrophic tubules with thickened basement membranes, lined with a single layer of atypical spermatogonia, displacing Sertoli cells towards the centre of the tubule. Borderline cases in which all of these criteria were not met were designated as "severe atypia". The only difference was the lack of complete rings of abnormal spermatogonia in the severe atypia group (Figs 1 and 2). Amongst 52 patients who had undergone orchiopexy and biopsy 40 patients were followed for a period of 15 to 92 months.

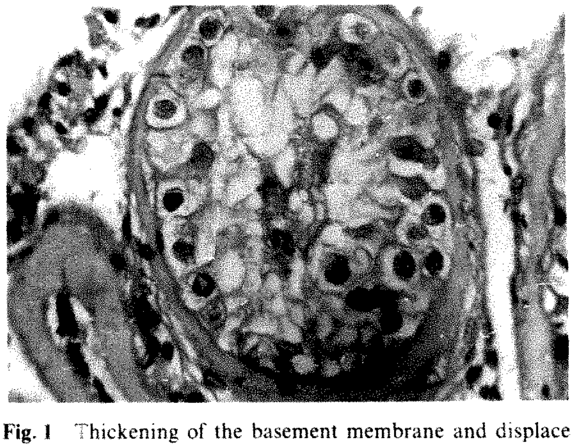

Fig. 1 Thickening of the basement membrane and displacement of Sertoli cells towards the centre of the tubule. (H and E ×600).

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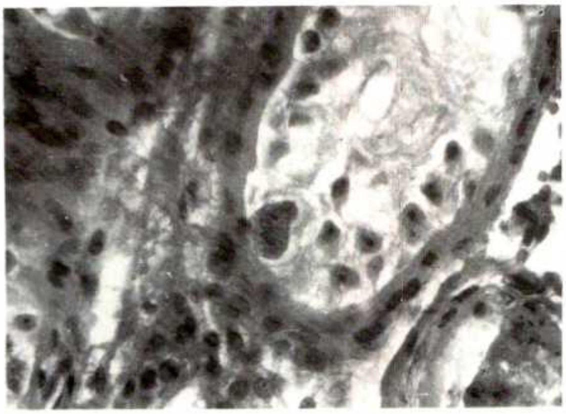

Fig. 2 Atypical germ cell with large nuclei is shown in the seminiferous tubule. (H and E ×600).

Results

CIS was not identified in any testis in this study. Borderline appearances of severe atypia were present in 5 patients (6.8%). When these findings were related to the site of the testis, it was found that only the abdominal testes showed the "Sertoli cell only" syndrome (Table).

Forty patients who had not undergone orchiectomy, including 5 with severe atypia, were followed up for 15 to 92 months and have shown no sign of invasive testicular tumour, all of them being asymptomatic.

Discussion

Although the association between CIS and testicular tumour has been reported in the literature (Waxman, 1976; Dorman *et al.*, 1979; Skakkebaek *et al.*, 1982; Pryor *et al.*, 1983), the natural history and significance of "severe atypia" or "atypical germ cells" is unknown. Aneiros *et al.* (1987) reported that 4 patients with atypical germ cells remained asymptomatic after a follow-up lasting between 39 and 51 months. Similarly, in another study, all of the patients with "severe atypia" were tumour-free (Ford *et al.*, 1985). In the present study, 5 patients with atypical germ cells who were followed up for a median of 18 months did not develop a testicular tumour.

Table Histopathological Findings According to the Site of the Testis

	High scrotal	*Inguinal*	*Abdominal*	*Total*
Sertoli cell only	—	52	8	60
Spermatogenetic arrest	5	12	—	17
Thickened basement membrane	3	5	—	8
Atypical germ cells	—	5	—	5
Total	8	74	8	90

Atypical germ cells may represent dysplastic cells or they may be a result of minor disturbance in the maturation. From this study there is no evidence to justify immediate orchiectomy for such a lesion, but further studies are required to determine the incidence and significance of this poorly understood entity.

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Contralateral Testicular Blood Flow during Unilateral Testicular Torsion

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Summary—Changes in contralateral testicular blood flow during unilateral testicular torsion were evaluated using an electromagnetic flowmeter in 13 adult male New Zealand White rabbits. There was an immediate and then a progressive decrease during torsion and a gradual increase following detorsion. A decrease in testicular blood flow over a critical period of time may be associated with contralateral testicular damage following unilateral testicular torsion.

Experimental and clinical studies have revealed that unilateral testicular torsion may result in contralateral testicular damage (Krarup, 1978; Nagler and White, 1982).

Although autoimmunisation (Williamson and Thomas, 1984; Madarikan, 1987), subclinical episodes of contralateral testicular torsion (Fraser *et al.*, 1985), underlying defects in spermatogenesis (Anderson *et al.*, 1986), the incidental occurrence of other conditions such as varicocele (Chakraborty *et al.*, 1985a) and the release of acrosomal enzymes (Wallace *et al.*, 1982) have been proposed to account for contralateral testicular damage, the mechanism still remains unclear. It is known, however, that one injured kidney can signal its distress to the other, which then develops anuria as a result of the decrease in blood flow (Hull *et al.*, 1980). In addition, the blood supply to the testis and the kidney is closely associated because of their common embryological origin (Tanagho, 1986).

It is therefore postulated that alterations in contralateral blood flow may play a part in contralateral testicular damage. An experimental study was designed to evaluate contralateral testicular blood flow in unilateral testicular torsion.

Material and Methods

A group of 13 adult male New Zealand White rabbits, previously reported to exhibit contralateral testicular damage following unilateral testicular torsion (Cerasaro *et al.*, 1984), was used. They were anaesthetised by intramuscular injection of pentobarbital. The testes were exposed through identical abdominoscrotal incisions. The right internal spermatic arteries were prepared in the same way in all animals. The probe was placed over the right internal spermatic artery and the right testicular blood flow monitored using a Biotronex Model 603 Electromagnetic Flowmeter.

Three rabbits served as controls. Blood flow through the right internal spermatic artery was monitored for 150 min without manipulation of the exposed left testis. The experimental group consisted of 10 rabbits. Each underwent clockwise 720° testicular torsion, which has previously been shown to cause contralateral testicular damage (Cerasaro *et al.*, 1984). The left testis remained twisted for 120 min. It was then untwisted and the blood flow through the right internal spermatic artery was monitored for a further 30 min.

Panelmeter values for right internal spermatic arterial blood flow were recorded throughout the procedure and any alterations resulting from left testicular manipulation were analysed by the paired *t* test.

Results

The 3 control rabbits showed only slight fluctuations in the right testicular blood flow.

In the 10 rabbits in the experimental group the

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initial right testicular blood flow value obtained from the panelmeter was 2.27 ± 0.28 ml/m. The flow fell to 1.57 ± 0.24 ml/m immediately after left testicular torsion, the difference between the initial and immediate post-torsion values being significant ($P < 0.01$). The blood flow then fell gradually during left testicular torsion and after 120 min had reached 1.19 ± 0.13 ml/m; this differed significantly from the immediate post-torsion value ($P < 0.01$). The blood flow in the right testis increased gradually after untwisting the left testis, reaching 1.74 ± 0.20 ml/m 30 min after detorsion. Although this value differed significantly from that obtained after torsion for 120 min ($P < 0.01$), there remained a significant difference between the value obtained initially and that obtained 30 min after detorsion ($P < 0.02$) (Table).

Discussion

Several direct and indirect methods can be used to measure testicular blood flow (Damber and Janson, 1977). Although there are limitations to the measurement of testicular blood flow using an electromagnetic flowmeter, it has been found satisfactory for monitoring alterations in flow through the internal spermatic artery.

Torsion produced an immediate and then a progressive decrease in the contralateral blood flow, while detorsion was followed by a gradual increase. Since the mass of tubules is the main determinant of testicular blood flow (Setchell and Galil, 1983), and contralateral damage occurs following torsion lasting for a critical period of time (Cosentino *et al.*, 1985), a steady decrease in blood flow over such a period of time may play a part in contralateral spermatogenic deterioration. Our findings are supported by previous reports which describe vascular disturbances and stagnation of blood in the contralateral testis (Chakraborty *et al.*, 1985b) and signs of ischaemia (Burge, 1987). In addition, a decrease in contralateral testicular blood flow has also been reported following other unilateral testicular events that may be associated with decreased fertility, such as efferent duct ligation (Wang *et al.*, 1985), cryptorchidism (Damber *et al.*, 1985) and varicocele (Sherins and Howards, 1986).

Table Blood Flow Values Recorded on the Panelmeter (× ±SE)

Left testicular manipulation	*Right internal spermatic arterial blood flow (ml/m)*
Initial	2.27 ± 0.28
Immediately after torsion	1.57 ± 0.24
After torsion for 120 min	1.19 ± 0.13
30 min after detorsion	1.74 ± 0.20

Regular blood flow is known to be the most important factor in normal spermatogenic function. Tubular damage in paraplegics (Ganong, 1971), increased blood flow to both testes following unilateral sympathectomy (Green *et al.*, 1985) and deterioration in testicular function with chronic adrenalin treatment (Damber and Janson, 1978) suggest that this regulation may be neurovascular. Since unilateral events also alter the contralateral testicular blood flow, a reflex arc as suggested by Mason (1981) might exist.

Afferent stimulus from the twisted testis produces a reflex decrease in contralateral testicular blood flow and a continuous decrease in blood flow over a critical period of time may cause contralateral spermatogenic deterioration.

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Treatment of Disseminated Germ Cell Tumours of the Testis

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Summary—Between 1979 and 1987 64 men with non-seminomatous germ cell tumours of the testis were treated with chemotherapy. Nearly half of these patients had large volume disease. The most frequently used combinations were VAB-6 and POMB/ACE. Chemotherapy lasted 3.9 months for small volume disease and 5.5 months for large volume disease. Seven patients (11%) underwent resection of residual masses; viable malignancy was found in only 1 of these. Relapse occurred in 6 complete responders, 3 of whom were salvaged with further chemotherapy. Fifty-three patients are presently alive and have received no treatment for periods of 5 to 86 months. Life table analysis forecasts a survival of 81%. Adverse prognostic factors have been recognised and include high initial serum concentrations of β-human chorionic gonadotrophin (β-HCG) and alpha fetoprotein (AFP), large volume disease and prior irradiation. Although the survival time of patients with advanced disease has improved in recent years, it remains considerably below that of patients who present with less advanced disease. Such patients should be treated aggressively from the outset in order to obtain maximum benefit from chemotherapy. Selected cases also require adjunctive surgery.

Malignant germ cell tumours are particularly aggressive neoplasms and until the past decade most patients with advanced disease died, survival times being short. However, it has long been recognised that this disease could respond dramatically to chemotherapy and a small proportion of patients could enter a sustained complete remission. Since the report by Li *et al.* (1960) with 3/23 (13%) complete remissions there have been major advances to the point where approximately 70% of patients are rendered disease-free with regimens containing cisplatin (Samuels *et al.*, 1975; Einhorn and Donohue, 1977; Newlands and Bagshawe, 1977; Einhorn and Williams, 1980; Vugrin *et al.*, 1983).

Disease-free status can be achieved but at the expense of considerable toxicity and morbidity which although fully justified for patients with advanced disease may not be necessary for those with less advanced disease.

We describe results obtained from our present policy of allocating low toxicity chemotherapy regimes to those patients with a good prognosis and high toxicity regimes to those patients judged to have a comparatively poor prognosis.

Patients and Methods

Patients

A series of 64 men with non-seminomatous germ cell tumours were treated between 1979 and 1987. Their median age was 28 years (mean 29, range 17–62). The primary sites were either testis (62 patients) or retroperitoneum (2 patients); 8 patients had received adjuvant irradiation after retroperitoneal lymphadenectomy (3 were stage I, 3 IIA and 2 were IIB). Radiotherapy included the para-aortic lymph nodes in 4 patients and, in addition, the mediastinal and supraclavicular nodes in the remaining 4 patients. All 8 patients received chemotherapy on relapse. Fifteen patients had undergone retroperi-

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toneal lymphadenectomy before the initiation of chemotherapy (3 patients were stage I, 2 IM, 5 IIA and 5 were IIB). This procedure changed the stage in only 1 patient (from IM to IIA). Two stage I patients received chemotherapy as adjuvant, 3 stage IIB patients because of incomplete resection of the para-aortic masses and the remaining 10 patients were given chemotherapy on relapse (including 1 stage I patient).

Staging

Staging included chest X-ray, CT scanning of the lungs and abdomen, bipedal lymphography, ultrasonography of the contralateral testis, full blood count, blood urea nitrogen and creatinine clearance, liver function tests, LDH, and measurement of serum AFP and β-HCG levels. In previous years, patients in apparent stage I disease had exploratory laparotomy and retroperitoneal lymphadenectomy. This procedure was also performed in order to decrease the tumour bulk before starting chemotherapy in patients with more advanced abdominal disease. CT scanning of the brain was done for specific indications and in recent years β-HCG and AFP concentrations in the cerebrospinal fluid (CSF) were measured routinely in patients with pulmonary metastases (Newlands *et al.*, 1983).

The Royal Marsden staging classification was employed (Peckham *et al.*, 1979).

Stage I	No metastases evident outside testis.
IM	No clinical evidence of metastases but raised levels of serum AFP and/or β-HCG after orchiectomy.
Stage II	Infra-diaphragmatic nodal metastases.
IIA	Metastases <2 cm diameter.
IIB	Metastases 2–5 cm diameter.
IIC	Metastases >5 cm diameter.
Stage III	Supra-diaphragmatic nodal metastases. Abdominal status 0 = negative lymphography. A, B, C, as for stage II.
Stage IV	Extranodal metastases.
IVL$_1$	Pulmonary metastases <3 in number.
IVL$_2$	>3 pulmonary metastases <2 cm diameter.
IVL$_3$	>3 pulmonary metastases, with at least one >2 cm diameter.
IVH+	Hepatic involvement. Abdominal status as for stage II.

Small volume disease included patients with Stage IM, IIA and B, IIIA and B and IVL$_1$ and IVL$_2$, A or B. Large volume disease included patients with Stage IIC, IIIC, IVL$_3$, IVL$_1$ and L$_2$ with C, and IV H+. By this classification the clinical stages on starting chemotherapy were IM (4), II (30) (A (8), B (17), C (5)), IIIC (2), IV (28).

Large volume disease was present in 30 patients (47%). β-HCG and AFP were measured by radioimmunoassay (normal range for β-HCG 0–5 IU/l and for AFP 0–5 KU/l). Raised levels of tumour markers were distributed as follows: β-HCG alone (9 patients), AFP alone (12), both β-HCG and AFP (22), making a total marker-positive rate of 67%.

Histology

Histology of the primary tumour according to the British Testicular Tumour Panel was: malignant teratoma intermediate (MTI) (12), malignant teratoma undifferentiated (MTU) (21), malignant teratoma trophoblastic (MTT) (18), combined tumours (CT) (13). One patient was treated with radiotherapy for pure seminoma and he developed a stage IM MTU in the contralateral testis 3 years later.

Treatment

All patients received cisplatin-containing chemotherapy. In previous years chemotherapy given in this department was based almost exclusively on the VAB-3 regime (8 patients) and the VAB-6 regime (28 patients). Four patients received the PVB and 24 the POMB/ACE regime. Since January 1986 patients have been allocated to receive VAB-6 (Table 1) (Vugrin *et al.*, 1983) if they present with small volume disease or POMB/ACE (Table 2) (Newlands *et al.*, 1983) if they present with large volume disease. To date, 17 patients have entered this protocol, 11 with small and 6 with large volume disease. The presenting stages were IIA (3), IIB (2),

Table 1 VAB—6 regime

Induction		
Day 1	Cyclophosphamide Vinblastine Dactinomycin Bleomycin*	600 mg/m^2 IV 4 mg/m^2 IV 1 mg/m^2 IV 30 mg IV push
Days 1–3	Bleomycin*	20 mg/m^2/day as a 24 h infusion × 3 days
Day 4	Cisplatin	120 mg/m^2 IV with mannitol-induced diuresis
	Every 3 weeks	

*Third induction without bleomycin

Table 2 POMB/ACE Regime

POMB	
Day 1	Vincristine 1 mg/m^2 IV at 10.00 h, methotrexate 100 mg/m^2 IV, start 15.00 h, followed by methotrexate 200 mg/m^2 as a 12-h infusion
Day 2	Bleomycin 15 mg as a 24-h infusion; folinic acid rescue started at 15.00 h in a dose of 15 mg 12-hourly for 4 doses
Day 3	Bleomycin infusion 15 mg as a 24-h infusion
Day 4	Cisplatin 120 mg/m^2 with hydration and mannitol diuresis
ACE	
VP 16-213 100 mg/m^2 IV, days 1-5; actinomycin D 0.5 mg IV days 3, 4 and 5; cyclophosphamide 500 mg/m^2 IV, day 5	
OMB	
Day 1	Vincristine 1.0 mg/m^2 IV at 10.00 h; methotrexate 100 mg/m^2 IV, start at 15.00 h, followed by methotrexate 200 mg/m^2 IV as a 12-h infusion
Day 2	Bleomycin 15 mg as a 24-h infusion; folinic acid rescue started at 15.00 h in a dose of 15 mg 12-hourly for 4 doses
Day 3	Bleomycin 15 mg as a 24-h infusion

The sequence of treatment schedules was 2 courses of POMB, followed by ACE. Subsequently POMB was alternated with ACE until patients were in biochemical remission as measured by HCG and AFP. The usual number of courses of POMB was 3 to 5. Patients were then continued on ACE alternating with OMB until biochemical remission had been maintained for approximately 12 weeks.

IV_0L_1 (4), $IVAL_1$ (2) for those with small volume disease and IIC (2), IIIC (1), $IVAL_3$ (1), $IVCL_1$ (2) for those with large volume disease. Raised levels of tumour markers on presentation were found in 7/11 (64%) and 5/6 (83%) patients respectively.

In previous years maintenance chemotherapy for 1 to 2 years was administered in 10 patients but since 1982 the duration of treatment has been adjusted to the individual patient according to disease volume and biochemical remission.

Using these criteria, chemotherapy for small volume and large volume disease lasted on average 3.9 and 5.5 months respectively. At present, if complete remission has been achieved no further treatment is given. If residual masses are present by imaging methods despite normal tumour marker levels, surgery is undertaken. When no tumour is identified in the surgical specimen no further treatment is given. When malignant cells are present, 2 to 3 additional cycles are administered.

Central nervous system (CNS) prophylaxis

Two patients developed CNS disease and died as a result whilst on treatment for pulmonary metastases. After 1985 we therefore adopted the policy of giving prophylactic chemotherapy to the CNS in patients presenting with lung metastases because of the increased risk of CNS involvement (Athanassiou *et al.*, 1983; Newlands *et al.*, 1983; Rustin *et al.*, 1986). These patients receive 3 intrathecal injections of methotrexate (12.5 mg) in addition to systemic chemotherapy. β-HCG and AFP levels in the CSF are measured routinely until serum marker remission and/or chest X-ray resolution.

Statistical methods

Survival rates were analysed by the Kaplan and Meier (1958) method. Differences in survival among patient subgroups were tested using the Kolmogorov-Smirnov test (Barr and Davidson, 1973).

Results

Of the 64 patients, 53 were alive for analysis on September 1, 1987. All are in complete remission and have received no treatment for periods ranging from 5 to 86 months (median 32). Neither coincidental nor treatment-related deaths occurred and no patient was lost to follow-up. Life table analysis projects a survival of 81% (Fig.). Survival according to disease volume and initial marker concentrations is shown in Table 3. Clinically bulky disease was present in 12 of 15 patients with β-HCG $>50{,}000$ IU/l or AFP >500 KU/l. Of the 8 patients who received radiotherapy before chemotherapy, only 4 are alive and well compared with 49/56 patients with no prior radiotherapy ($P=0.01$). Three of 4 and 1 of 4 patients with small and large volume disease respectively are alive and in complete remission.

All 17 patients (11 allocated to VAB-6 and 6 to POMB/ACE according to disease volume) have

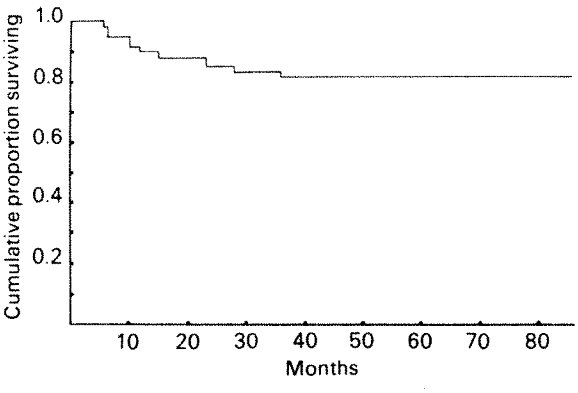

Fig. Survival of 64 patients treated between 1979 and 1987.

Table 3 Survival in Relation to Tumour Volume and Initial Marker Concentrations

Patient group	*No. of patients*	*NED (%)*	
SVD	34	33(97)	$P=0.001$
LVD	30	20(67)	
β-HCG and/or >50,000 IU/l AFP > 500 KU/l	15	9(60)	$P=0.001$
β-HCG and/or <50,000 IU/l AFP < 500 KU/l	49	44(90)	

NED: no evidence of disease.
SVD: small volume disease.
LVD: large volume disease.

been in complete remission for periods ranging from 5 to 17 months (median 13).

Post-chemotherapy surgery

Seven patients (11%) underwent post-chemotherapy surgery because of radiological evidence of residual tumour. None had elevated tumour markers at the time of surgery. Three were found to have fibrotic tissue, 3 differentiated teratoma and 1 showed histological evidence of residual malignant teratoma plus differentiated tissue. This patient was given 3 additional courses of chemotherapy. All are alive and disease-free at 26, 27, 29, 40, 52, 54 and 72 months.

Relapses

Six patients relapsed after apparent complete remission (Table 4); 3 are alive and well at 20, 42 and 49 months after cessation of salvage chemotherapy. Relapses occurred at 3, 5, 7, 11, 13 and 18 months from the time of discontinuation of primary chemotherapy.

Toxicity

Routine blood counts for all patients showed a mean nadir of 2.55×10^3 for WBC and 115×10^3 for platelets in those patients with small volume disease and 2.2×10^3 and 105×10^3 respectively for those with large volume disease. Prior irradiation proportionally favoured more severe myelosuppression in patients with large volume disease (mean nadir 1.7×10^3 for WBC and 86×10^3 for platelets). Febrile episodes associated with neutropenia occurred in 19 patients (29%) and they were treated successfully with broad spectrum antibiotics. Ten patients (15%) required blood transfusion at some time during their chemotherapy because of pronounced anaemia. Renal function was tested routinely in all patients. Blood urea nitrogen and creatinine clearance were estimated before each cycle and blood urea nitrogen and serum creatinine were estimated every 10 to 12 days. No permanent renal damage was seen, although slight and transient deviation of renal function (WHO grade 1) occurred in 12 patients (19%). Similarly, no bleomycin-related lung toxicity was encountered as judged by routine chest X-ray before each course. Reversible (WHO grade 1) peripheral neuropathy was observed in 6 patients (9%). Audiometry was not done routinely except in 5 patients with obvious high frequency hearing loss. In 2 the damage was permanent. All patients suffered grade 2 to 4 nausea and vomiting.

Discussion

The aim of chemotherapy in patients with testicular germ cell tumours is to achieve stable complete remission. Several cisplatin-based schedules have been developed within the last few years. Attempts to improve both survival figures and to overcome drug resistance led to the incorporation of etoposide in drug combinations (Newlands and Bagshawe, 1977; Williams and Einhorn, 1980; Peckham *et al.*,

Table 4 Relapse in 6 Patients in Relation to Stage, Histology, Initial Chemotherapy, Stage on Relapse, Salvage Chemotherapy and Final Outcome

Pt	*Stage*	*Histology*	*1st chemo.*	*Stage on relapse*	*Salvage chemo.*	*Outcome*
1	$IVCL_1$	MTU	VAB-3	$IVBL_3$	P+E	D
2	$IVCL_2$	MTU	VAB-3	IVL3, H+	VAB-6+E	D
3	IVL_3	MTU	VAB-6	IVL_3	P+E+ADRIA	NED
4	$IVBL_1$	MTU	VAB-6	IIC	EPOMB	D
5	$IVCL_1$	MTT	VAB-6	$IVCL_1$	POMB/ACE	NED
6	IIB	CT	VAB-6	IVL_3	POMB/ACE	NED

NED: No evidence of disease.
D: dead.
P: cisplatin.
E: etoposide.

1983) and this has proved of value in terms of achieving higher complete response rates in patients with advanced and bulky disease (Newlands *et al.*, 1983; Ozols *et al.*, 1983; Peckham *et al.*, 1983; Logothetis *et al.*, 1985). However, high-risk patients continue to have a poorer prognosis and more intense treatment is needed from the onset.

Several prognostic factors have been identified (Bagshawe and Begent, 1983; Bosl *et al.*, 1983; Medical Research Council Working Party on Testicular Tumours, 1985) and we were able to find a strong correlation between survival and initial serum concentrations of β-HCG and AFP. In this series, 15 patients with HCG $>50{,}000$ IU/l or AFP >500 KU/l showed a survival rate of only 60% in contrast with a survival rate of 90% in 49 patients with lower concentrations or no marker production ($P=0.001$). On the other hand, there were no differences in survival between patients with positive or negative tumour markers. The disease volume on presentation was also a very accurate predictor of survival (small versus large volume disease, $P=0.001$).

Although it has been reported that hepatic and brain involvement is not a serious prognostic factor (Newlands *et al.*, 1983), of the 4 patients presenting with liver metastases only 1 is alive and well; the 2 patients with CNS metastases have both died. All of these patients were treated several years ago with less intensive chemotherapy and the sole survivor was the first patient to receive etoposide (POMB/ACE) from the onset. It is therefore quite possible that these failures should be attributed to inappropriate chemotherapy. The 2 patients with CNS involvement developed metastases while on treatment for L_1 and L_2 disease. They did not receive CNS prophylaxis, which is now used in patients presenting with lung disease and/or HCG $>1{,}000$ IU/l. Since this introduction we have not seen such patients developing brain metastases during treatment.

In this series, radiotherapy before chemotherapy was a definite adverse prognostic factor strongly affecting patients with large volume disease. Although this group is small and accurate conclusions are difficult to draw, the figures obtained (50% NED in previously irradiated patients compared with 88% NED in those with no irradiation ($P=0.01$)) may be attributed to the difficulty in administering subsequent chemotherapy because of severe myelosuppression. Non-irradiated patients received courses of chemotherapy at mean intervals of 20 days (small volume disease) and 22 days (large volume disease). The corresponding intervals for those who received irradiation were 21 and 29 days. Reduction of doses was necessary for at least 2 courses for all 4 irradiated patients with large volume disease and 1 with small volume disease. Septicaemic episodes also occurred at least once in the 4 patients with large volume disease and in 2 of those with small volume disease. Although not achieving statistical significance, there was a trend indicating more treatment failures in patients with undifferentiated malignant teratoma.

The present series covers a considerable length of time and differences may have existed in terms of integrated treatment in general (or chemotherapy in particular) as therapeutic attitudes in germ cell tumours have changed. In this department, primary retroperitoneal lymphadenectomy is no longer performed as it is now clear that the final outcome is unaffected (Javadpour *et al.*, 1982; House *et al.*, 1983). The policy is now to resect any residual tumour at the end of chemotherapy. In this way surgery may improve the complete response rate by an additional 15 to 30% (Vugrin *et al.*, 1981; Jones *et al.*, 1982; Vugrin *et al.*, 1983; Logothetis *et al.*, 1986) and identify the need for further chemotherapy in those patients with a still viable tumour.

Radiotherapy has also been abandoned, although it may retain a role for patients with malignant teratomas unresponsive to chemotherapy. Our patients have received several schedules of cisplatin-containing combination chemotherapy in the past. Currently, patients with small volume disease receive the less aggressive but highly effective VAB-6 regime, whereas those with large volume disease receive POMB/ACE.

The aim is to avoid excessive toxicity and morbidity in patients with a good prognosis without jeopardising their excellent prospects of a cure. Alternatively, etoposide could be used in such patients in case of drug resistance or relapse. In this way we were able to reduce septicaemic episodes to 3 (6%) from a total of 49 courses of chemotherapy involving 11 recent patients with small volume disease. None of these patients needed a reduction in dosage or delay in treatment and no treatment failures were observed.

In the 6 recent patients with large volume disease, septicaemia occurred in 5 of 42 courses (12%) and dose reduction was necessary in 2 patients for 1 and 2 courses respectively. Again, no treatment failures were observed, thus providing justification for this approach. Despite major advances in the management of germ cell tumours, a small proportion of patients still die. Problems such as "the appropriate treatment for the appropriate patient", drug resistance and treatment of relapses await their final solution. This, it is hoped, will emerge from those centres specialising in the management of this highly curable disease.

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Cisplatin-based Chemotherapy does not Eliminate the Risk of a Second Testicular Cancer

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Summary—Of 781 patients with germ cell cancer, 14 developed a second (subsequent) testicular cancer during follow-up. The incidence was not related to the treatment of the first germ cell cancer. In particular, adequate cisplatin-based chemotherapy did not reduce the risk of developing a second tumour. Screening programmes in patients with previous germ cell tumours should include *all* patients, irrespective of prior treatment.

Patients with unilateral testicular cancer have an increased risk of developing a second germ cell cancer in the remaining testis (Dieckmann *et al.*, 1986; Hargreave, 1986; Kristianslund *et al.*, 1986; von der Maase *et al.*, 1986b). In 50% of patients the second testicular tumour appears within 5 years of the diagnosis of the first germ cell tumour. It is believed that it develops from a pre-malignant condition, carcinoma *in situ* (von der Maase *et al.*, 1986a). Carcinoma *in situ* of the contralateral testis can be demonstrated in about 5% of patients with newly diagnosed testicular cancer (von der Maase *et al.*, 1986b) and it has also been demonstrated in 8 of 15 previously untreated patients with extragonadal germ cell tumours (Daugaard *et al.*, 1987).

It is probable that testicular carcinoma *in situ* is not spontaneously reversible. The optimal treatment of this condition is not yet defined, but radiotherapy is currently recommended (von der Maase *et al.*, 1986b) except in patients with testicular carcinoma *in situ* who are to be treated by cisplatin-based chemotherapy because of the advanced stage of their first germ cell tumour. Preliminary experience indicates that chemotherapy eradicates carcinoma *in situ* in most cases (von der Maase *et al.*, 1985). If this hypothesis is correct, one would expect a lower incidence of subsequent testicular carcinoma after cisplatin-based chemotherapy than after other treatment in patients with germ cell cancer. To test the hypothesis we analysed the incidence in consecutive patients with germ cell cancer who had undergone different types of treatment.

Patients and Methods

From 1979 to 1987, 784 patients were referred to the Norwegian Radium Hospital (NRH) with newly diagnosed testicular tumours (766) or extragonadal germ tumours (18). All patients were staged according to the Royal Marsden classification system (Peckham *et al.*, 1981); 3 patients were subsequently excluded because they were found to have bilateral testicular cancer at the time of the initial diagnosis.

Biopsy or ultrasonography of the remaining testis was not routinely performed. Patients with seminoma stage I and IIA/B were treated by abdominal radiotherapy (36–40 Gy). Early in 1979 patients with non-seminoma clinical stage I also received radiotherapy. During 1979 this policy was changed and these patients subsequently underwent retroperitoneal lymph node dissection (Fosså *et al.*, 1988). No further treatment was given if no metastases were found in the biopsy specimen. In 1987 16 non-seminoma patients with clinical stage I were included in a surveillance protocol (no treatment, observation only). Non-seminoma patients with metastases, seminoma patients with clinical stage > IIC and relapsing patients received cisplatin-based chemotherapy (Fosså *et al.*, 1988). All those with extragonadal germ cell tumours were

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treated with cisplatin-based chemotherapy.

The patients were grouped as follows:

Group I: no cytotoxic treatment (134 patients).
Group II: radiotherapy only (326).
Group IIIa (testicular cancer): chemotherapy ± radiation (303).
Group IIIb (extragonadal germ cell tumour): chemotherapy ± radiotherapy (18).

The patients' records were reviewed with regard to a history of undescended testis, the presence or absence of an atrophic contralateral testis and/or fertility. Patients were regarded as fertile if they had fathered children before or after the diagnosis of their first germ cell tumour and/or if they were normospermic according to seminal fluid parameters (Fosså *et al.*, 1984).

Routine follow-up (to 31 December 1987) comprised clinical, radiological and biochemical tests at intervals of 2 to 6 months but not testicular ultrasonography. Only if clinical examination suggested a subsequent tumour were further investigations performed (ultrasonography, biopsy).

Results

Fourteen of the 781 patients developed a second testicular tumour (Table 1). Although the numbers within each group were small there seemed to be no difference between the incidence in Groups II and III (a and b combined). Only 1 patient in Group I developed a second tumour.

Judged by the accumulated cisplatin doses, all patients received adequate chemotherapy for their first germ cell cancer (3–8 cycles) (Table 2). There was no statistical difference between the time intervals from the first to the second germ cell tumour in Groups I and II (combined) when compared with Group III (a and b combined) (Mann Whitney test); 3 of the 14 patients with a second tumour were known to have a high risk of developing testicular cancer: either an atrophic remaining testis or a history of undescended testis (Table 2).

Table 1 Incidence of Second Testicular Cancer in Relation to Prior Treatment of First Germ Cell Malignancy (NRH, 1979–1987)

Treatment		*Patients under observation*	*Second testicular cancer (%)*
No cytotoxic treatment			
Group I		134	1 (0.8)
Radiotherapy only			
Group II		326	7 (2.1)
Chemotherapy ± radiotherapy			
Group III	a	303	5 (1.7)
	b	18	1 (5.6)
	Total	321	6 (1.9)
Total		781	14

Discussion

In calculating the incidence of second testicular tumours *all* patients referred to the NRH were considered without taking into account that about 5% of the patients in Group III had died within 2 years of the diagnosis of the first germ cell tumour. If this had been considered, the incidence would have been 2% in Group III (combined). Furthermore, if the patient with carcinoma *in situ* is excluded from Group II, the incidence for Groups II and III would become even more similar. In the present series the total incidence is lower than in previous reports (Dieckmann *et al.*, 1986; Kristianslund *et al.*, 1986; von der Maase *et al.*, 1986b). However, the observation time for many of our patients is relatively short and a higher incidence is expected with longer follow-up.

The most important observation in the present study is the finding of a similar incidence of second testicular tumours in patients after prior cisplatin-based chemotherapy and in those after radiotherapy. According to von der Maase *et al.* (1986b), many invasive testicular tumours develop from a pre-invasive carcinoma *in situ* stage, but the exact percentage of invasive germ cell tumours arising from carcinoma *in situ* is not known. Although no biopsy was performed at the time of the initial diagnosis and no ultrasonography was done, one may assume that some of our patients with a second tumour had carcinoma *in situ* in the remaining testis when the first germ cell tumour was diagnosed. If one accepts this assumption and also that the majority of invasive tumours develop with a background of carcinoma *in situ*, it becomes evident from the present study that cisplatin-based chemotherapy does not eradicate carcinoma *in situ*, at least not permanently. It does not seem to prevent the development of a second testicular tumour. This is in agreement with reports of residual germ cell cancer in orchiectomy specimens obtained after intensive chemotherapy (Fowler *et al.*, 1979; Greist *et al.*, 1984; Chong *et al.*, 1986). Both in the present study and in a report by Chong *et al.* (1986), mature testicular teratoma was a relatively frequent find-

Table 2 Details of Patients

					First germ cell tumour			*Second (subsequent) testicular cancer*		
Patient No.	*Age (years)*	*Undescended testis*	*Infertility*	*Atrophic testis*	*Histology*[1]	*Stage*	*Treatment*	*Time interval (months)*	*Histology*	*Stage*
Group I: No cytotoxic treatment (134 patients)										
1	22	no	?	no	EC+TER	I	RLND[2]	4	EC+TER	I
Group II: Radiotherapy only (326 patients)										
2	42	no	no	yes	SEM	I	36 Gy	6	SEM	I
3	39	no	?	no	SEM	I	36 Gy	5	SEM	I
4	24	no	?	no	SEM	I	36 Gy	8	Ca. in situ	I
5	42	no	no	no	SEM	I	36 Gy	31	SEM	I
6	31	no	?	yes	SEM	I	40 Gy	48	SEM	I
7	42	no	no	no	SEM	I	40 Gy	58	SEM	I
8	27	no	no	no	EC+TER	I	50 Gy	70	EC+TER	I
Group IIIa: Chemotherapy ± radiotherapy (testicular) (303 patients)										
9	22	yes	?	no	EC	IV	800[3] (4)	4	TER (mat)	II
10	19	no	no	no	EC+TER	IV	850 (6)	51	EC	II
11	18	no	no	no	EC	II	495 (3)	52	EC+CHOR	II
12	26	no	?	no	EC+TER +Y	IV	720 (4)	62	EC+SEM	II
13	16	no	?	no	EC+TER	II	700 (4)	82	SEM	I
Group IIIb: Chemotherapy ± radiotherapy, (extragonadal) (18 patients)										
14	28	no	?	no	TER (mal)	II	2025 (8)	30	TER (mat)	I

1. SEM: seminoma. EC: embryonal ca. Y: yolk sac tumour. CHOR: chorioca. TER: teratoma, mature (mat) or with malignant transformation (mal).
2. Retroperitoneal lymph node dissection.
3. Accumulated cisplatin dose (mg) (number of chemotherapy cycles).

ing, indicating that the chemotherapy nevertheless had some influence on tumour development in the remaining testis. Residual mature teratoma is frequently found in metastases from germ cell cancer after effective chemotherapy (Hendry *et al.*, 1981; Donohue *et al.*, 1982; Fosså *et al.*, 1988). Williams *et al.* (1987) also suggested that second testicular tumours occur as often in patients undergoing chemotherapy as in those without chemotherapy.

Another explanation of our observations may be possible: the incidence of testicular carcinoma *in situ* may be much higher in advanced metastatic testicular cancer than in non-metastatic non-seminoma or in early seminoma. The surprisingly low incidence of second testicular tumours in Group I may partly support this view. If chemotherapy is given for metastases from the first germ cell tumour, some of the patients with carcinoma *in situ* in the remaining testis are cured, but not all. This leads to a similar incidence of subsequent testicular cancer in the radiotherapy and chemotherapy groups. This hypothesis of a particularly high incidence of carcinoma *in situ* in metastatic non-seminoma and its possible cure by chemotherapy in some patients would be in agreement with a preliminary report by von der Maase *et al.* (1985). Further prospective studies comprising biopsies from the remaining testis in all patients with unilateral testicular cancer will prove whether this hypothesis is true and whether testicular carcinoma *in situ* is particularly often found in patients with advanced stages of their first germ cell cancer.

From a practical point of view the present study indicates:

1. In patients with germ cell cancer there is no difference in the incidence of a second testicular

tumour as a result of previous treatment. In particular, cisplatin-based chemotherapy does not eliminate the risk of developing a second tumour.

2. Retrospective and prospective screening programmes in patients with a prior germ cell malignancy should be employed in *all* patients irrespective of previous treatment.

Addendum

While preparing this report we became aware of 3 additional patients with germ cell cancer who developed a second testicular tumour 1, 3 and 4 years after adequate cisplatin-based combination chemotherapy given between 1979 and 1980; 2 patients had a testicular tumour at the time of the initial diagnosis and 1 had an extragonadal germ cell tumour. These patients had been treated for their first tumours in 1972, 1977 and 1978 respectively and were therefore not included in the present series.

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Injury to the Prepuce

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Summary—Injury to the prepuce is uncommon. A total of 32 patients were treated within a 3-year period. A difference in the aetiology between boys and adults was noted. Accidental injury to the prepuce occurred in 6 boys, with zipper injuries being the commonest among children. Coital and self-inflicted injuries accounted for 85% of adult cases. In patients with coital injuries, predisposing phimosis or a short frenulum was common.

Penile injuries have been reported to be uncommon (Selikowitz, 1977). Over the years, much attention has been directed towards erectile tissue injury of the penis (Pryor *et al.*, 1981) but there are no reported series on injury to the prepuce itself, which presumably is considered to be rare. We report a group of patients with isolated preputial injury. The aim of the review was to study the cause and management of preputial injury in children and adults.

Patients and Methods

The Kwong Wah Hospital is a 1600-bed institution with an annual admission rate of about 60,000 patients. Within a period of 3 years, July 1984 to June 1987, 32 patients with injuries to the prepuce were admitted to the Department of Surgery through the Accident and Emergency Department. A retrospective analysis of their hospital records was performed. The aetiology was studied and the injury classified.

Results

The mechanisms of injury were classified into 4 types: coital, self-inflicted, direct assault and accidental. The youngest patient was aged 4 and the oldest 37 years (mean 23).

Paediatric group

There were 6 patients below 12 years of age who were admitted to the paediatric surgical ward. They all had accidental injuries.

The commonest cause of preputial injury in children was the zipper (4 out of 6 patients) (Fig. 1). The prepuce was accidentally trapped between the sliding piece and the teeth of the zipper. In 2 patients the prepuce was trapped while the zipper was being opened and the other 2 were injured while the zipper was being fastened. These patients had phimosis and typically had not put on underpants. The parents' attempts to free the patients had failed and the preputial skin had been jammed

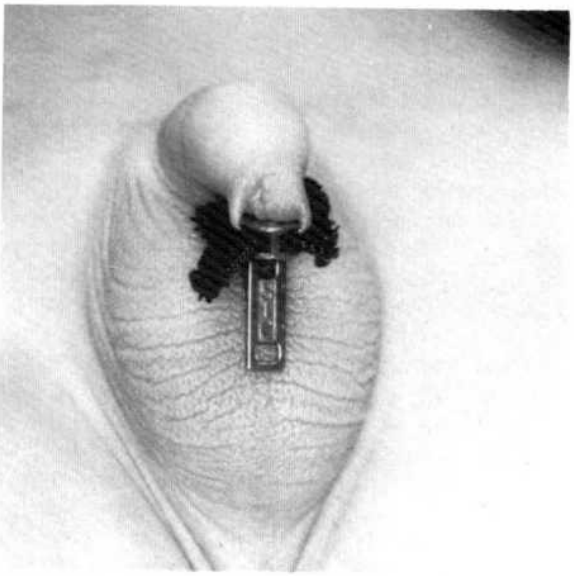

Fig. 1 Prepuce trapped on sliding piece of zipper.

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even tighter. Reduction of the trapped prepuce was successful in 1 patient by moving the zipper tooth by tooth; circumcision was performed 2 weeks later for the phimosis. In the other 3 patients the prepuce was tightly trapped. Circumcision was performed as an emergency after the trousers had been cut away from the zipper.

An 8-year-old boy sustained preputial injury when the unbalanced toilet seat crashed down upon his genitalia. He had a 1-cm longitudinal laceration over the dorsum of the prepuce. There was no injury to the glans penis. In view of the presence of phimosis, circumcision was performed.

A 9-year-old boy was accidentally kicked by his classmate on his genitalia during a soccer match. There was only superficial abrasion over the tip of the preputial skin. The patient was treated conservatively with a hibitane dressing.

Adult group

There were 26 adult patients with injury of the prepuce; 15 had sustained the injury during coitus and 7 had a self-inflicted injury. There were 2 patients with preputial injuries as a result of direct assault and in 2 patients the injuries were accidental.

Of the 15 patients with coital injury, only 2 were married and they sustained the injury during coitus with their wives; 3 patients sustained the injury during coitus with prostitutes. Two types of injuries were recognised—a transverse laceration in the prepuce and a tear in the frenulum. Eight patients sustained transverse lacerations. Phimosis was present in 6 patients, in 2 of whom the prepuce actually fused with the glans penis (Fig. 2). The other 2 patients had a long redundant prepuce. All 8 patients required circumcision.

Of the 7 patients with a tear in the frenulum (Fig. 3), 4 were found to have a short frenulum and frenuloplasty was performed. In the other 3 patients the laceration was sutured.

Seven patients had self-inflicted injuries: 3 had a tear in the frenulum and 4 had transverse lacerations in the prepuce. No underlying anatomical abnormality was found in this group of patients. Simple suturing was performed in all cases.

There were 2 patients with preputial injuries as a result of direct assault. The first patient was attacked by his fellow worker in a factory. He sustained 2 transverse lacerations in the prepuce when he was stabbed by a sharp triangular-shaped instrument (Fig. 4). The weapon pierced his trousers and lacerated the prepuce. Suturing was performed for the lacerations. The second patient was beaten up by other people. He received multiple kicks over his genitalia. He had bruises over his inner thighs and a 1.5-cm laceration over his prepuce. There was no other injury to the scrotum or the penis. The wound was sutured.

One patient slipped and fell in the bathroom. His penis hit the toilet flush tank handle. A haematoma collected in his prepuce, which was evacuated. In

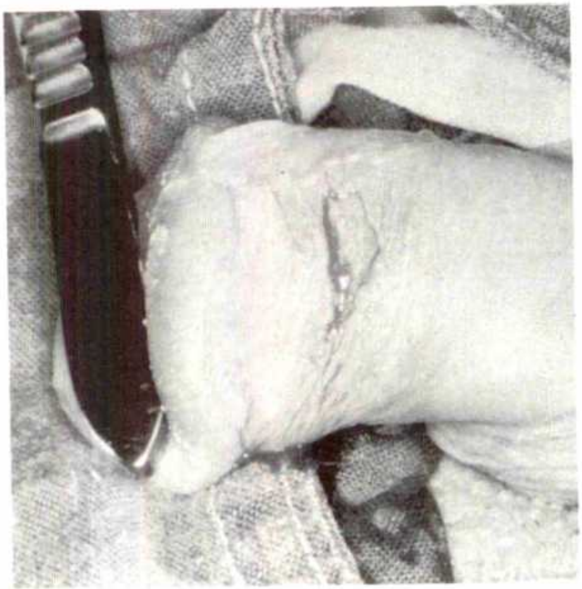

Fig. 2 Transverse laceration of the prepuce with adhesion between the prepuce and the glans penis.

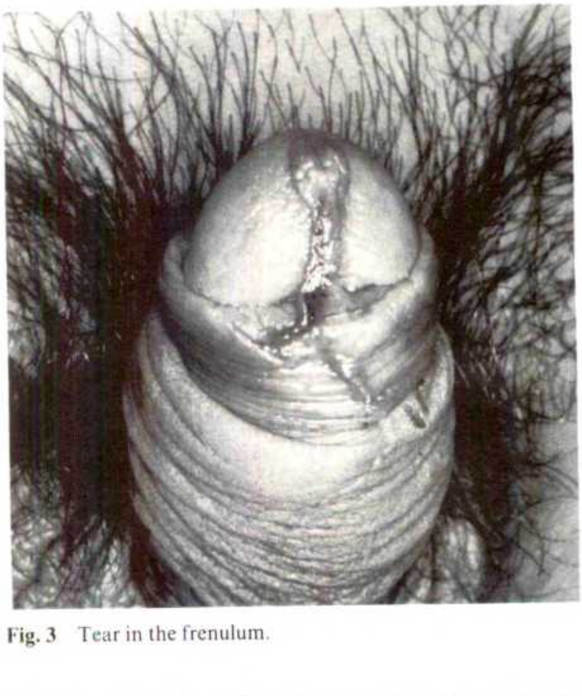

Fig. 3 Tear in the frenulum.

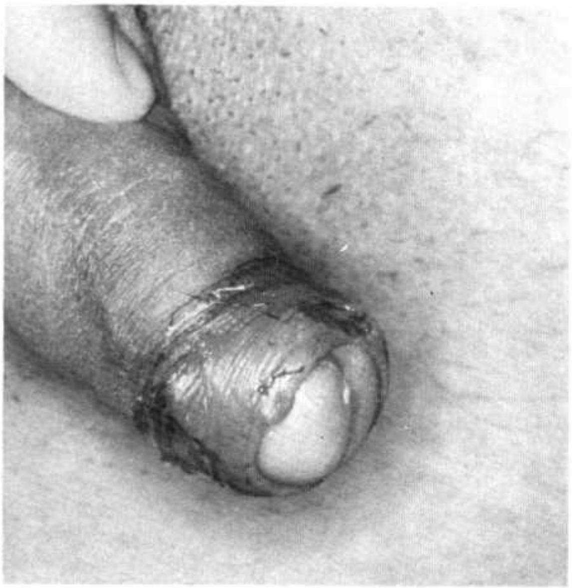

Fig. 4 Transverse laceration in the prepuce after direct assault.

the last patient the prepuce was caught in the zipper. He had phimosis and circumcision was performed.

All patients were followed up 2 weeks and 3 months after discharge. No urological problem was detected and coitus had been resumed in all adult patients at the last follow-up.

Discussion

Penile injuries were classified by Pryor *et al.* (1981) into 4 types according to the anatomical structures involved: skin, erectile, urethral and complex injuries. Injury to the prepuce constituted only a specific group of patients with penile skin injury. The prepuce is defined as the fold of skin covering the neck of the penis which overhangs the glans penis for varying distances. The preputial skin is remarkable for its thinness and its great mobility. These factors account for the vulnerability of the preputial skin to injury.

We have treated 32 patients with preputial injuries during a 3-year period. The injury was more common in the adult group (81%), especially in those who were sexually active. Six boys sustained a preputial injury. It was noted that the mechanisms of injury differed significantly between the paediatric and adult groups.

There are few case reports on injury of the prepuce in the paediatric group. Zipper injury, direct trauma and toilet pan injury have been reported (Ezell *et al.*, 1969). Human bites (Siang, personal communication) and the battered child syndrome (Slosberg *et al.*, 1978) have also been associated with preputial injuries.

Zippers are potentially dangerous to boys who are apt to zip up in a hurry and in the present series they account for most paediatric cases. These patients usually have phimosis and have not put on underpants, which accounts for the ease with which the prepuce comes into contact with the zipper. There are 3 methods of managing zipper injuries. Firstly, with a co-operative patient, reduction by manipulation, moving the zipper tooth by tooth, can be achieved as in 1 of our patients. Secondly, the median bar of the sliding piece of the zipper can be cut with a bone cutter (Flowerdew *et al.*, 1977). Thirdly, in patients with phimosis, we advise performing circumcision after cutting the trousers away from the zipper. Plastibell should not be attempted and circumcision with trimming of the prepuce should be done. Despite all these methods of treatment, prevention is still preferable. Zipper injuries can be prevented if the manufacturer adds a protective flap inside the line of the zipper.

With regard to the toilet pan injury, the seat and lid design constitute a hazard to young boys. A change of design, in which the lid is in a reclining position rather than a vertical one when lifted up, would help. Placement of the flush tank away from the bowl is one design which gives the lid a more stable equilibrium.

In adults, 85% of preputial injuries are related to various sexual practices. Direct assault and accident account for only a small proportion of cases.

Coital injury is the commonest injury in adults (50%). It usually occurs at the initial phase of coitus. There is usually a combination of symptoms with severe pain after penetration and bleeding on withdrawal. Because of the pain, rapid detumescence would also be noted. The mechanism of injury is due to forceful penetration of the penis. Most patients would admit that there was a lack of sexual arousal of the partner. We can recall no case of coital injury due to any particular extravaganza. These patients usually present immediately to the Accident and Emergency Department.

In coital injury, 2 patterns can be found: the transverse laceration of the prepuce and the tear in the frenulum. In both types of injury some underlying anatomical abnormalities are noted. Phimosis or a long redundant prepuce are found in patients with a transverse laceration. In 2 patients with adhesions between the glans penis and the prepuce, the injuries were more severe. We advise circumcision for this group of patients. Of the 7 patients with tearing of the frenulum, 4 were found to have a short and tight frenulum. The tethering effect of the short frenulum during penetration was presumably the cause of the injury. There was no associated phimosis or redundant prepuce. Circumcision in these patients is not necessary. The transverse tear should be sutured longitudinally so that the frenulum can be lengthened.

All self-inflicted injuries of the prepuce occurred during a search for sexual excitement, although these patients denied the use of special instruments. Citron and Wade (1980) described the popular use of the vacuum cleaner. No underlying anatomical abnormality was detected in this group of patients. Both transverse laceration of the prepuce and tearing of the frenulum were noted, the type of injury depending on the manipulation by the individual. Suturing is sufficient treatment for these patients.

Isolated preputial injury can also occur as a result of direct assault and by zipper accident.

In conclusion, boys and adults have different causes of injury to the prepuce. In boys, zipper injury is the commonest cause. Coital injury accounts for the majority of cases in the adult and one must be aware of associated anatomical abnormalities in order to institute the correct treatment.

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Pharmacocavernometry: a Modified Papaverine Test

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Summary—The papaverine test has become established in the investigation of impotence. Although a full response to papaverine excludes a significant vascular lesion, failure to respond may be due to either arterial deficiency or venous leakage. Pharmacocavernometry, which combines the papaverine test and an artificial erection test, was performed in 126 patients. Intracorporeal pressure was monitored following the intracorporeal injection of 80 mg papaverine; 10 min later, saline was infused to determine the presence of a venous leak. Five different responses were observed. Patients with a Type 1 or 2 response were psychogenic or neurogenic. Patients with a Type 3 response were arteriogenic and patients with a Type 4 or 5 response had significant venous leakage. The modified papaverine test permits more information to be gained concerning the aetiology of the impotence.

Since intracorporeal papaverine was first shown to produce an erection (Virag, 1982), the papaverine test has become an established technique in the diagnosis of erectile dysfunction, although it has not yet been standardised. There is also an incidence of prolonged erection or subsequent fibrosis (Padma-Nathan *et al.*, 1987). The interpretation of a papaverine test is difficult and whilst a full response does exclude a significant vascular lesion, the meaning of an impaired response is uncertain. Some men with psychogenic impotence and normal erectile function on nocturnal penile tumescence (NPT) fail to respond to papaverine and this may be a result of anxiety (Buvat *et al.*, 1987). An impaired response may also be due to abnormality of the arterial supply or to leakage from the erectile tissue. Venous leakage may be confirmed by cavernometry (Wespes *et al.*, 1984), when a high flow is required to create and maintain an artificial erection and early filling of the veins is seen on cavernography. Radiology is necessary only for those patients where operative treatment is being considered. There is no standardisation of these techniques or agreement as to whether the test should be performed with or without intracorporeal papaverine. Furthermore, the significance of venous leakage as diagnosed by these methods has still to be determined. This report describes a test which can be performed as an out-patient procedure and combines the papaverine test and cavernometry in an attempt to gain more information regarding the aetiology of the impotence.

Patients and Methods

The test was performed on 126 patients, aged 22 to 77 years (mean 51.8), referred to St Peter's Hospital or the Lister Hospital with impotence and in whom the aetiology of the problen was in doubt; 33 patients were diabetic and 6 had Peyronie's disease. All patients underwent a standard assessment consisting of case history and physical examination, measurement of serum testosterone, prolactin and blood glucose.

The modified papaverine test was performed under aseptic conditions after the injection of 2 ml of 1% lignocaine. One corpus was punctured dorsolaterally just proximal to the coronary sulcus with a 19 F butterfly cannula. Intracorporeal pressure was monitored through the cannula connected via a 3-way tap to a pressure transducer. Penile girth was monitored throughout the procedure using a PERIN II gauge (Desai *et al.*, 1988). The

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initial intracorporeal pressure (p0) was recorded and 80 mg papaverine injected via the 3-way tap and massaged along the shaft of the penis. The highest intracorporeal pressure reached during the next 10 min was noted (p10). The quality of the erection was graded as Grade 0—no tumescence, Grade 1—slight tumescence, Grade 2—moderate tumescence which was considered adequate for penetration, and Grade 3—full erection.

A second 19 F butterfly cannula was then inserted into the other corpus (Fig. 1) and normal saline infused at a flow rate of 40 ml/min until a rigid erection was observed and the intracorporeal pressure was over 110 mm Hg. The infusion rate was slowly reduced until the pressure remained steady. This maintenance flow (fm) provided a measure of the venous outflow from the penis. On occasions when the initial flow rate was insufficient to produce a full erection the flow rate was increased, up to a maximum of 120 ml/min, and the intracorporeal pressure and quality of erection noted.

The perfusion was then stopped, the pressure fall observed and the steady end pressure recorded (pend). In about one-third of patients the pressure remained above 50 mm Hg and the corpus was aspirated until there was complete detumescence. Both cannulae were then removed and firm pressure applied until any bleeding stopped. The patient was then allowed to go home but warned to return if the erection recurred and lasted for more than 4 h.

Results

All but 1 patient with full erection following papaverine injection had an intracorporeal pressure rise to over 50 mm Hg. Figure 2 shows that there is good correlation between the grade of erection and

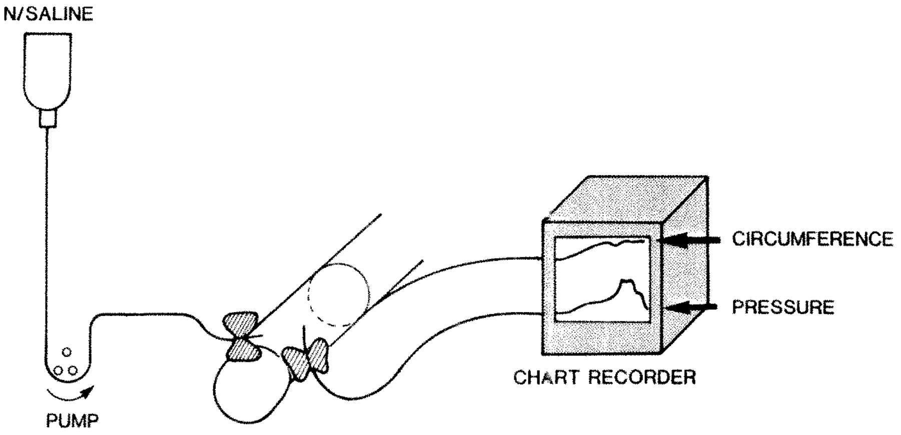

Fig. 1 Equipment.

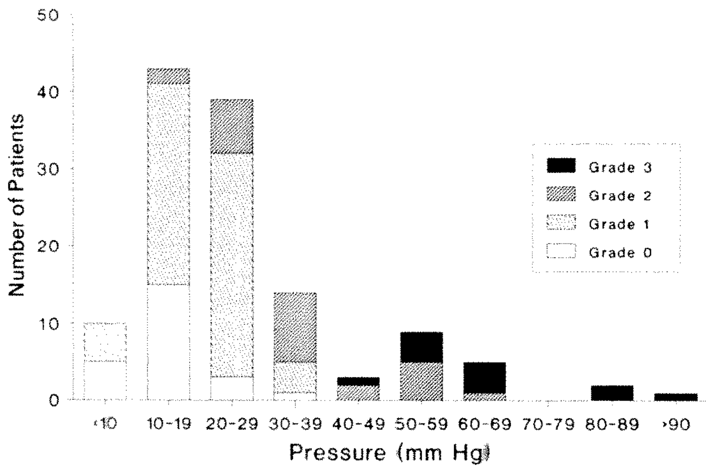

Fig. 2 Grade of erection plotted against intracorporeal pressure (maximum pressure in first 10 min [p10] following papaverine injection).

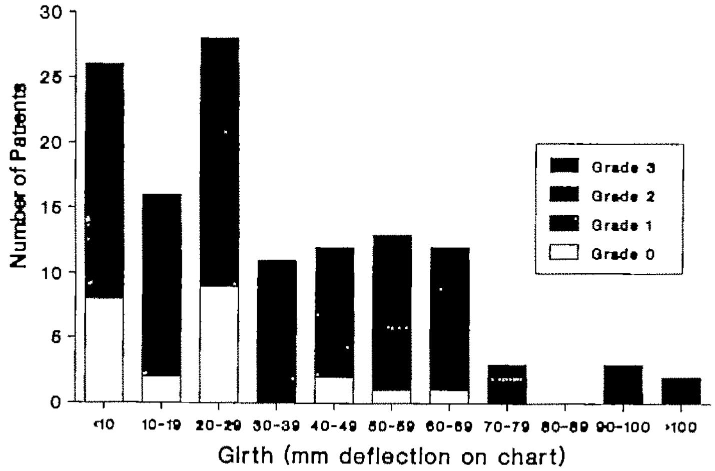

Fig. 3 Grade of erection plotted against increase in girth (maximum increase in first 10 min following papaverine injection).

the highest intracorporeal pressure attained in the first 10 min (r = 0.777). Conversely, Figure 3 shows only slight correlation between the grade of erection and the increase in girth (r = 0.313).

The changes in intracorporeal pressure following the papaverine injection and cavernometry show 5 distinct pressure response patterns. The numerical results of the trends in these groups are shown in the Table.

Type 1 response

The typical response in this group of patients is shown in Figure 4. All patients had a pressure rise of more than 50 mm Hg following injection of papaverine. The initial intracorporeal pressure of the non-erect penis is recorded at point A (p0). Following the injection of 80 mg papaverine (B) there was a characteristic rise in pressure to over 50 mm Hg (p10 at point C). Initiation of perfusion (point D) resulted in a rapid rise in the intracorporeal pressure. Full rigidity was shown by a reduction in girth due to lengthening of the penis and possible compression of the tunica albuginea. Flow was reduced until the pressure remained steady at above 110 mm Hg (point E). The flow to maintain this pressure was recorded (fm) and was less than 25 ml/min in all patients. When the perfusion was stopped (point F) the pressure fell to a steady end state pressure (pend at point G). For all the patients in this group the penis remained erect and the intracorporeal pressure was greater than 50 mm Hg. It was necessary to aspirate up to 120 ml of fluid before complete detumescence took place. The erection did not recur in any patient.

This type of response was found in 17 patients, 14 of whom were considered to have psychogenic impotence on the basis of the history and other findings. Three diabetic patients were considered to have neurogenic impotence as there was evidence of autonomic neuropathy.

Type 2 response

In this group the intracorporeal pressure following the papaverine injection was less than 50 mm Hg and a full erection (grade 3) only occurred in 1 of these patients. The changes in pressure and girth

Table Results of 126 Patients Undergoing Modified Papaverine Test

	n	*Age*	*P0* *mm Hg*	*P10* *mm Hg*	*Pend* *mm Hg*	*FC* *ml/min*	*FM* *ml/min*
Type 1	17	42.35	8.23	61.35	71.09*	30.64*	10.09*
Type 2	22	51.86	8.41	27.19	63.27	38.18	11.41
Type 3	47	53.70	10.19	20.68	24.66	55.78	23.43
Type 4	21	54.34	8.38	15.33	17.43	98.09	73.00
Type 5	19	52.84	6.79	13.47	12.73	120	No erection

* n = 11.

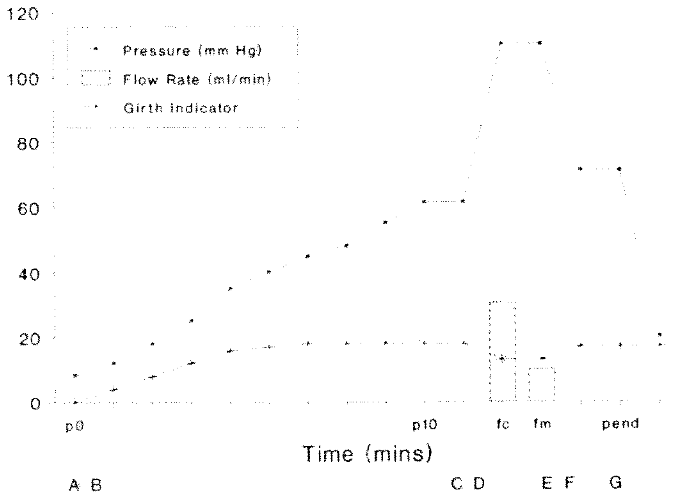

Fig. 4 Type I response seen in 17 patients (mean values plotted). p0—initial intracorporeal pressure. p10—maximum intracorporeal pressure in first 10 min. fc—flow to create erection. fm—flow to maintain erection. pend—steady end pressure following cessation of perfusion. A—Initial pressure. B—Injection of 80 mg papaverine. C—maximum pressure in first 10 min. D—Initiation of perfusion. E—Measurement of maintenance flow. F—Cessation of perfusion. G—Measurement of steady end pressure.

are shown in Figure 5. During perfusion the mean maintenance flow rate was 11.4 ml/min (range 0–31). When stopped the penis remained erect with an intracorporeal pressure greater than 50 mm Hg. All patients required aspiration before detumescence occurred.

In this group of 22 patients, 5 were considered to have a neuropathy (3 were diabetic, 1 had undergone an abdominoperineal resection of rectum and 1 suffered from myalgic encephalomyelitis). The other 17 were considered to have psychogenic impotence.

Type 3 response

The typical response in this group of patients is shown in Figure 6. None of these patients achieved full erection before or after perfusion. In addition to these criteria the flow required to maintain the erection during perfusion was less than 50 ml/min. Of the 47 patients in this group who failed to respond to papaverine, 8 were thought to have a psychogenic cause for their impotence on the basis of the history. There were 14 diabetic patients in this group and in 4 of these there was evidence of a neuropathy.

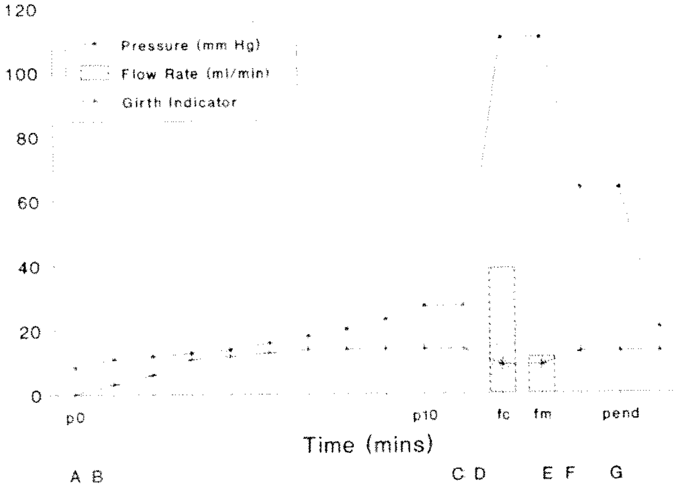

Fig. 5 Type 2 response seen in 22 patients.

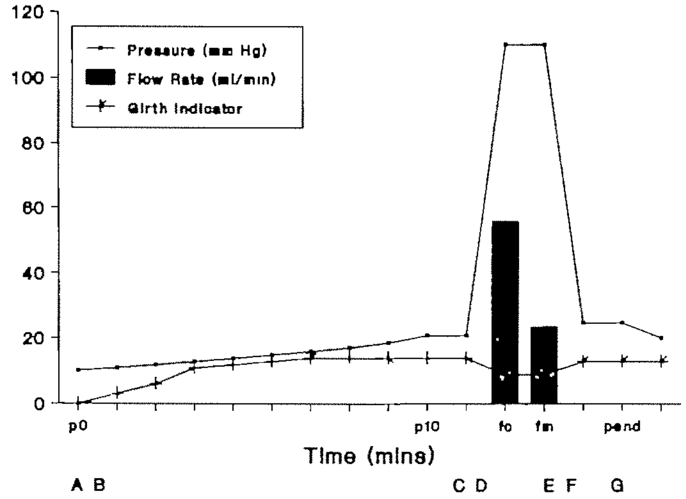

Fig. 6 Type 3 response seen in 47 patients.

Type 4 response

In this group of 21 patients there was a poor response to papaverine (Fig. 7) and the flow required to maintain the erection was greater than 50 ml/min. Complete detumescence occurred following cessation of the perfusion. All 21 patients in this category were initially judged to have an organic cause for their impotence.

Type 5 response

The 19 patients in this group (Fig. 8) had only slight tumescence with papaverine (grade 0–1) and perfusion failed to produce a full erection at the maximum flow rate of 120 ml/min. All of the patients were considered to have organic impotence from the history and in many cases the erectile dysfunction had always been present.

Complications

One patient had some extravasation of saline after replacement of the first butterfly cannula. The fluid reabsorbed and there were no sequelae. No patient had a prolonged erection or subsequent evidence of fibrosis.

Discussion

The evaluation of impotence using papaverine alone and the artificial erection test alone has been

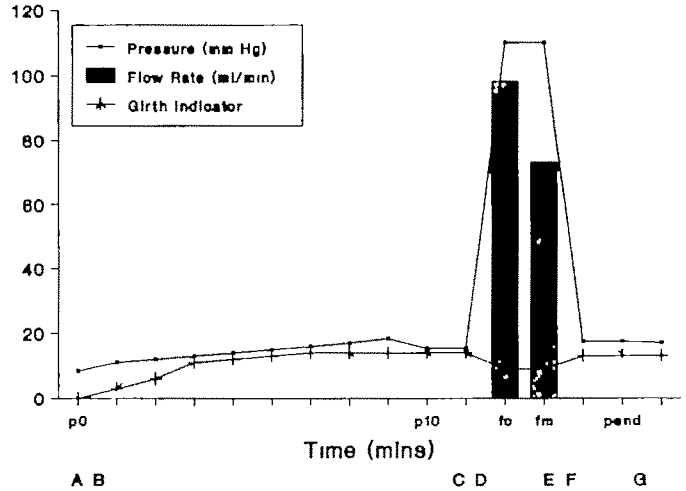

Fig. 7 Type 4 response seen in 21 patients

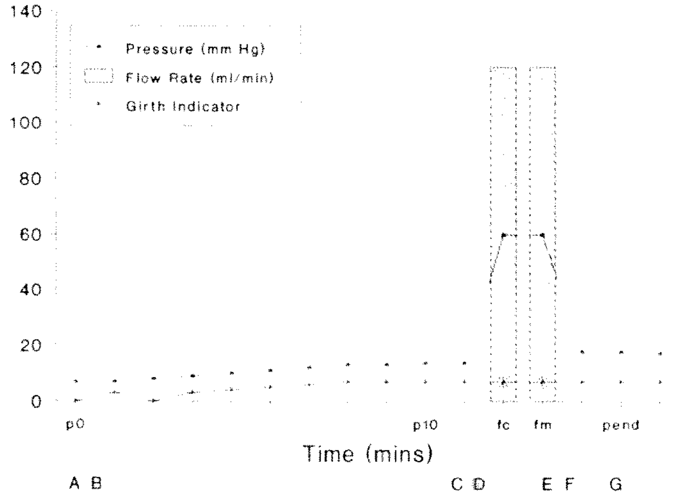

Fig. 8 Type 5 response seen in 19 patients.

recorded with variable results. Wespes *et al.* (1986) used pharmacocavernometry and concluded that little additional information was gained, although less fluid was required to produce an erection. Lue *et al.* (1986) concluded that using both papaverine and the artificial erection test gave a more physiological response. Many patients now receive papaverine as part of their routine investigation and this should be combined with an artificial erection test in those who do not respond fully. This might enable the clinician to differentiate between arteriogenic and venogenic impotence.

The mechanism of erection has not yet been clearly elucidated but it seems that both an increase in arterial perfusion and a decrease in venous outflow are necessary. Papaverine has been shown to act on both of these mechanisms (Delcour *et al.*, 1987) and this accounts for the popular use of this drug in the diagnosis of vasculogenic impotence. The normal response to papaverine is a rise in intracorporeal pressure and should this not occur, an arterial deficiency and/or venous leakage is usually found. The history must be taken into account as the occasional false negative response may be due to anxiety.

Freidenberg *et al.* (1987) noted 5 different responses but combined Types 3, 4 and 5 into a single category which they judged to show vasculogenic impotence. We agree that patients with Type 1 and 2 responses do not have a vasculogenic basis for impotence. It is unnecessary to perform a perfusion study in Type 1 patients as the penile response to intracorporeal papaverine is a full erection. Patients with a Type 2 response have a full erection after perfusion and Freidenberg stated that these patients had full erections when they performed intracavernosal self-injection of papaverine at home. This observation is confirmed in the present study. It is possible that the impaired response during the modified papaverine test was due to stress. Buvat *et al.* (1987) found that up to 30% of patients with psychogenic impotence failed to respond to papaverine. The modified papaverine test permits diagnosis of these patients who do achieve an erection after perfusion. Patients with this type of response do not have a significant vascular basis for their impotence.

Freidenberg *et al.* (1987) stated that patients with Types 3, 4 and 5 responses all had a vasculogenic cause for impotence and we agree. The diagnosis of venous leakage is difficult but all authors would agree that if the infusion of large volumes of fluid fail to produce an erection, there must be a venous leak. Type 5 patients fall into this category. There is discussion about the perfusion rate necessary in order to justify the diagnosis of a venous leak. The time taken to create an erection on infusion of the corpus varies and is dependent on flow rate. However, the maintenance flow rate is more constant for any given patient and it is this measurement that is considered to be of diagnostic importance. Wespes *et al.* (1986) showed that patients without a venous leak had a mean flow to maintain erection of 6.7 ml/min (range 5–10). The mean of our Type 1 and Type 2 patients was 10.97 ml/min (range 0–31). We have taken a perfusion rate of more than 50 ml/min to maintain erection as being diagnostic of a venous leak. This means that patients with a Type 3 response are considered to have arteriogenic impotence. However, it is not possible to exclude an arteriogenic element to the impotence of those patients with Type 4 and 5 responses. Crude Doppler examination of the penile vasculature may produce useful information but more precise blood flow measurement using Duplex ultrasound scanning (Lue *et al.*, 1985) or Doppler wave form analysis (Desai *et al.*, 1987) may permit this. It is necessary to pursue the cause of impotence in young patients only where vascular reconstruction may be indicated or in those who are candidates for venous ligation surgery. Many patients do not wish to proceed to any form of surgery and many are content with the implantation of penile prostheses, particularly in view of the fact that venous surgery has a success rate of only 50%.

The modified papaverine test offers additional information about the aetiology of impotence and is a useful out-patient procedure. It is possible to perform cavernography at the conclusion of the test.

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Use of the "Correctaid" Device in the Management of Impotence

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Summary—A series of 20 unselected patients with impotence of various aetiologies were given a custom fitted external erection assistance device, the Correctaid. They have been followed up for 14 months. Only 4 patients are still using the device regularly to attain satisfactory intercourse and a further 4 use it occasionally. This device is a useful, non-invasive alternative for the treatment of impotence in well selected, motivated patients and their partners.

A normal penile erection depends on an increase in arterial flow, relaxation of the corporeal smooth muscle, an increase in intracorporeal pressure and venous outflow restriction. The neurotransmitter which produces these events is not known but they can be reproduced by the intracavernosal injection of vasoactive drugs (Virag, 1982). An erection can also be produced by creating a vacuum around the penis, and this is sustained as long as the vacuum is maintained. The "Correctaid" erection assistance device (Synergist Ltd, Houston, Texas) (Fig.) consists of a soft, transparent sheath of silicone rubber with a side arm to allow air to be withdrawn to produce a vacuum. When applied to the flaccid penis and air withdrawn the penis enlarges to fill the device, allowing intercourse to take place. It is reusable and worn during intercourse.

We report our experience of the device in patients with impotence of various aetiologies.

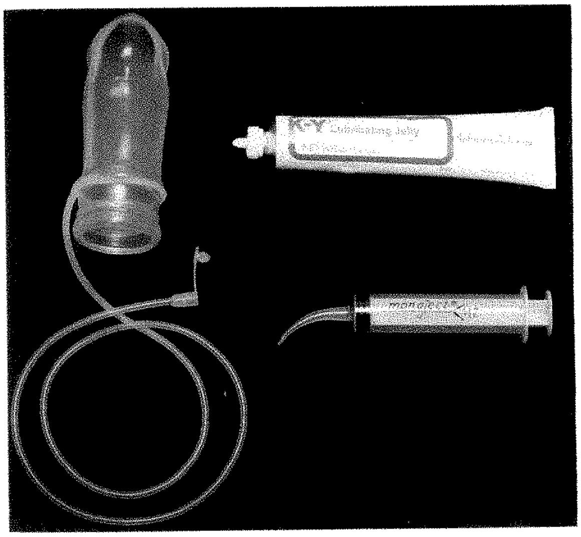

Fig. "Correctaid" device. Silicon sheath with flexible collar at base to act as a seal and tubing for creating vacuum.

Patients and Methods

The device was given to 20 patients. All underwent a full medical investigation, including assessment of their endocrine status, Doppler studies of the penile arteries and their response to a pharmacologically induced penile erection. The predominant cause of their impotence was classified as psychogenic (9), arteriogenic (4), neurogenic (4) and venous leak (3).

A correctly fitting prosthesis was provided for each patient, depending on penile length and circumference. He was taught how to use the device but was not seen with his partner. Patient and partner experience was assessed by questionnaire or direct questioning. Two patients have been studied by digital subtraction dynamic cavernosograms while using the device.

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Results

Only 4 patients still use the device on a regular basis (at least once a week) and they would recommend it to others. An additional 4 patients use the device occasionally; 3 of these felt it was too complicated and took too long to set up, by which time they had often lost their desire; 2 of these 4 patients also found that the device was too thick and diminished sexual sensation. Of the 8 patients who have continued to use the device, 5 described their erections as good and 3 described them as satisfactory. Nine patients used the device on at least 1 occasion but abandoned further use because it took too long to set up, was too complicated and its thickness diminished sensation. Three also commented that they found the device unnatural, since it took the spontaneity out of intercourse and was contrary to their idea of natural intercourse. Three patients never used the device because their partners found it unacceptable. Of the 3 patients with venous leaks only 1 uses the device regularly and obtains a satisfactory erection.

No patient complained of bruising or penile oedema after using the device. The partners of the 8 patients who still use it find it satisfactory and experience neither discomfort nor trauma from its use. None reported diminished sexual sensations. The partners of 2 patients who no longer use the device complained of discomfort with its use and refused to accept it. All 4 patients who use the device regularly have an organic basis for their impotence.

Discussion

Most of the successful treatments available for impotence are invasive and are associated with significant complications. An incidence of up to 40% has been reported with implants (Kaufman *et al.*, 1982). Intracavernosal injection of vasoactive drugs, though highly effective, is an invasive technique and a low incidence of cavernosal fibrosis has been reported (Zorgniotti, 1986).

The creation of a vacuum around the flaccid penis to produce erection is not new. In 1917, Lederer patented one such device and others have patented modifications of this system (Nadig *et al.*, 1986). The "Erecaid" is a vacuum device which relies upon a tourniquet placed around the proximal penile shaft to maintain the erect state. The erection is not always sufficiently hard for intercourse and may decrease further within 5 to 10 min. Bruising due to the tourniquet has also been reported (Nadig *et al.*, 1986). In a recent study (Wiles, 1988), an "Erecaid" system was used by 10 selected diabetic patients with impotence; 9 were reported to have used it successfully, although 3 partners were not satisfied and refused to answer the questionnaire designed to assess the results. The follow-up in that study was only 3 months.

The "Correctaid" device reported in the present study is worn during intercourse and relies upon a custom fitting to maintain the vacuum and erection. Dynamic cavernography was performed in 2 patients while using the device. This revealed partial occlusion of superficial and deep dorsal veins seen on the control film. As these veins were not completely occluded, there was no risk of impairing the penile circulation and so the period for which it could be worn was unlimited.

This study shows the importance of selecting well motivated patients and their partners. Those studied in this series were unselected and often poorly motivated, particularly in the psychogenic group. Furthermore, the availability of alternative forms of treatment in this unit meant that some patients were keen to try them. As a result, only 4 used the device for 14 months on anything approaching a regular basis. Of these, 2 wish to use alternative methods.

It was concluded that this device is suitable as an alternative to intracavernosal autoinjection or penile implants. Full counselling of the patient and his partner is required to achieve optimum results. The device may be useful for patients with premature ejaculation because erection can be maintained for unlimited periods of time. However, its usefulness in this particular condition needs to be further evaluated.

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Case Reports

Haemangiopericytoma of the Bladder

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Haemangiopericytoma arising from the urinary bladder has not previously been reported.

Case Report

A 30-year-old woman was admitted in acute urinary retention with a 3-week history of frequency and pain on micturition. A catheter specimen of urine grew 10^5/ml *Staphylococcus aureus* but all other investigations were normal. She was treated with trimethoprim, following which she was able to pass urine normally. Two years later she re-presented in acute retention with sterile urine. Intravenous urography outlined a 6-cm round filling defect of the bladder. Cystoscopy confirmed a smooth discrete tumour arising from the trigone which was treated by complete transurethral resection. Histology showed many vascular channels with connective tissue sheaths prominent on reticulin staining and surrounded by numerous ovoid and spindle-shaped pericytes (Figs 1 and 2). After 2 years of cystoscopic follow-up one recurrence was resected transurethrally, but no further recurrence has been seen and chest X-ray has remained clear during a total follow-up of 4 years.

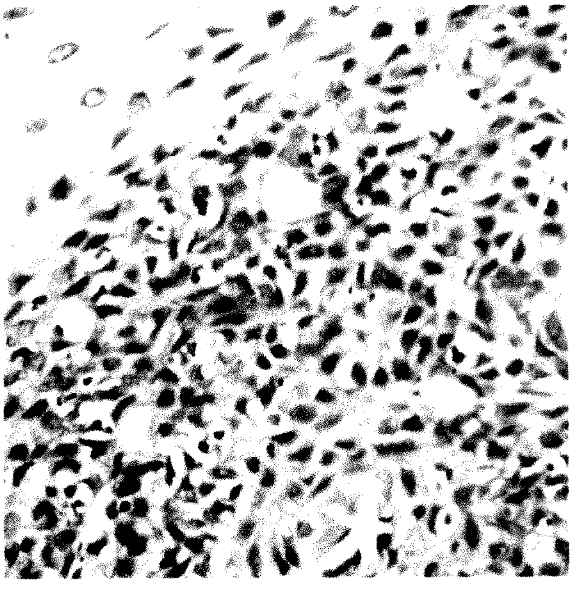

Fig. 1 Paraffin section of haemangiopericytoma of the bladder, stained with haematoxylin and eosin (× 250).

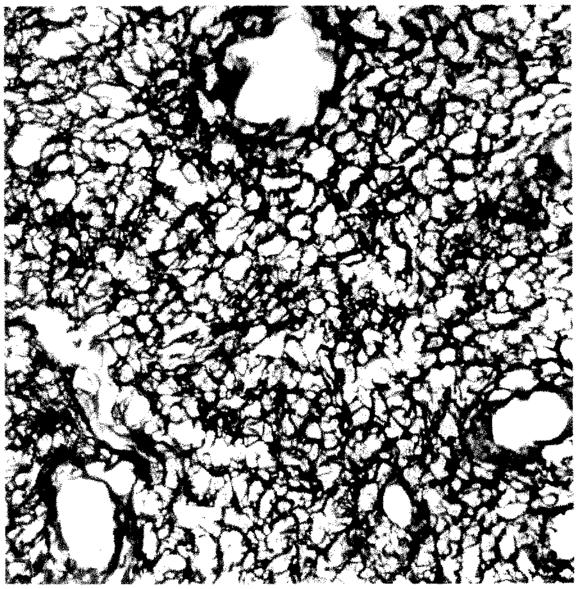

Fig. 2 Serial paraffin section taken from the same block as Figure 1, showing characteristic reticulin pattern of the tumour by means of a silver stain (× 250).

Comment

Haemangiopericytoma was first described by Stout and Murray (1942) as a rare and distinct vascular neoplasm derived from pericytes. Presentation can occur at any age, more commonly in the lower extremities or pelvis, less often the head, neck or trunk (Poole *et al.*, 1979). Previous reports of this tumour invading the urinary bladder do not confirm this organ as the site of origin (Prout and Davis, 1977). Symptoms relate to the tumour location but may develop late since growth is often slow and painless. There is little distinction between benign and malignant forms; 50% may recur and metastasise to the lungs or skeleton (Poole *et al.*, 1979). Surgical ablation is the preferred treatment since response to radiotherapy and chemotherapy is usually poor.

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Jogger's Phimosis

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Conditions related to jogging have been reported, such as jogger's nipples (Levit, 1977) and penile frostbite (Hershkowitz, 1977).

Case Report

A 47-year-old man was referred by his family doctor with a diagnosis of "long-standing constrictive balanitis" which caused him pain on erection but no other problems. One year earlier he had been out jogging (wearing a jogging suit) in freezing weather and had developed a painful sensation at the tip of his penis. The incident left him with a non-elastic foreskin that interfered with his sexual activities. Examination and subsequent circumcision revealed a glans and foreskin without subjective evidence of balanitis but a considerable degree of phimosis.

He made a satisfactory recovery from circumcision and has resumed jogging, though he now gives more thought to dressing according to the weather.

Comment

This man apparently suffered frostbite to the foreskin that healed with fibrosis and led to phimosis and erectile difficulty. Outdoor sportsmen in cold climates should be warned about penile frostbite as a consequence of not wearing sufficiently warm clothing.

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Testicular Seminoma in an Immunosuppressed Renal Transplant Recipient

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Immunosuppressive therapy increases the susceptibility to cancer (Penn and First, 1986). Malignant tumours have been encountered in up to 4.5% of renal transplant recipients (Birkeland, 1983), which implies a significantly increased risk of cancer in these patients. Skin cancer is the most frequent malignancy in these cases, followed by haematological neoplasms and solid tumours. Testicular cancer in this context is unusual, with approximately 20 cases reported to date (Frantz *et al.*, 1985).

Case Report

At the age of 38 years the patient was in end-stage renal failure and undergoing chronic haemodialysis. One year later he was given a cadaveric renal transplant. Two acute rejection episodes were treated by methylprednisolone and for the next 4 years his immunosuppressive therapy consisted of azathioprine and methylprednisolone. He then had 2 further rejection episodes and received high dose steroids. Increasing side effects, however, led to the administration of cyclosporin A only. Slightly impaired graft function at the age of 44 years was followed by the finding of a fist-sized right testicular mass. A right orchiectomy was performed.

Histological examination (Fig.) and staging showed the tumour to be a pure seminoma pT3 NO MO. Radiation therapy of 32 Gy was given to the right iliac region and retroperitoneum with shield protection of the graft on the left side Two years later the patient was well with slightly elevated creatinine.

Comment

The aetiology of malignancies in renal transplant recipients is thought to be secondary to impaired immunosurveillance (Birkeland, 1983). Tumours with a suspected viral aetiology are amongst the neoplasms seen most frequently in these patients (Kinlen, 1982). Penn and First (1986) observed an excessive number of neoplasms in endocrine organs after the administration of cyclosporin A and questioned its possible hormonal effects in the aetiology of these tumours.

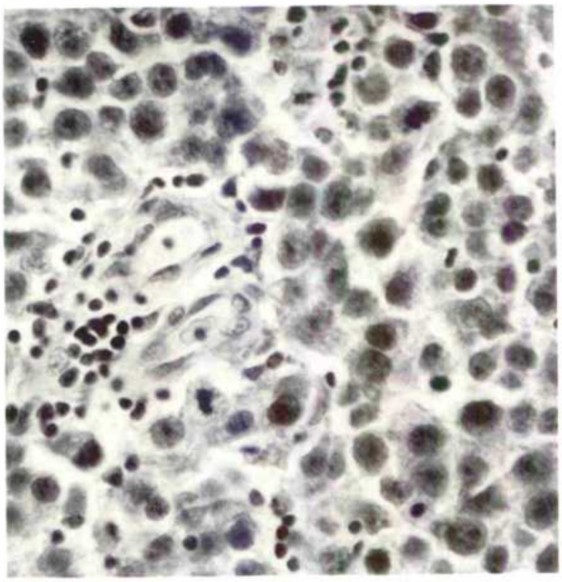

Fig. Typical seminoma with scanty lymphocytic infiltration. Most of the tumour cells contain large round nuclei, with prominent nucleoli. Note mitoses within this field. (H and E × 350).

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Congenital Pyelolymphatic Fistula in a Child with Chyluria

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We report a child with chyluria due to a congenital pyelolymphatic fistula who showed an initial favourable response to renal pedicular ligation and stripping. The essential investigations to establish the diagnosis are urine microscopy and bilateral ascending lymphangiography.

Case Report

A 5-year-old boy presented with a 1-year history of passing milky urine with intermittent chylous clots.

Urine microscopy demonstrated a very high cellular content with a predominance of small lymphocytes. The urinary lipid concentration was high (4.3 g/l) but the calcium/creatinine ratio, amino acids and protein values were within normal limits. Serum urea and electrolytes, albumin, total protein, cholesterol, triglycerides and creatinine clearance were also within the normal ranges. The full blood count was normal and urine culture did not yield any growth. Radiological investigations included chest radiographs, intravenous urogram, cystoscopy and bilateral retrograde pyelograms, and renal ultrasound. All failed to demonstrate either a cause or the site for the chyluria. Bilateral ascending lower limb lymphangiograms demonstrated a lymphatic fistula between the retroperitoneal lymphatics and the left renal pelvis (Fig.).

The left kidney was explored and dilated subcapsular lymphatics and chyle in the renal pelvis were observed. The lymphatics around the renal pedicle were ligated and stripped from the vessels. The patient was discharged after 7 days without passing any further chyluria. At home 2 days later, however, chyluria returned, though to a lesser degree. Thereafter he has been managed conservatively with a high protein, low fat, vitamin-supplemented diet, and remains well at follow-up with moderate chyluria and no chylous clots.

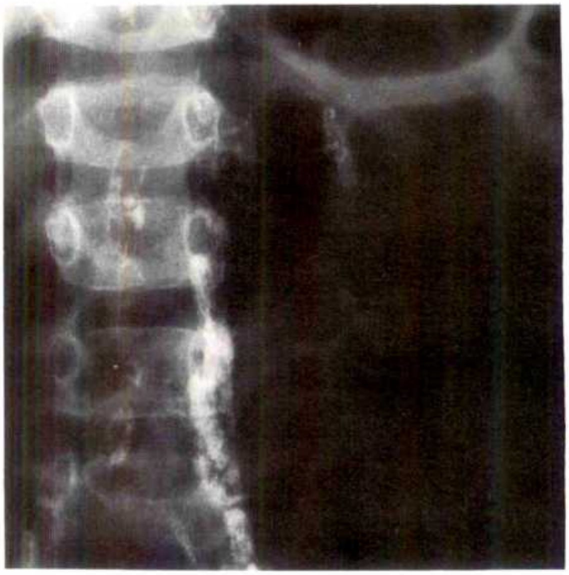

Fig.

Comment

Chyluria is extremely rare in childhood and in Western countries, but worldwide the commonest cause is filarial infestation (Yamauchi, 1945). Non-parasitic chyluria may occur due to congenital lymphangiomas of the urinary tract, traumatic lymphangio-urinary fistula or obstruction of the thoracic duct.

The single most important radiological investigation to demonstrate the site of leakage is an ascending lymphangiogram (Ngan *et al.*, 1977). The rarity of this condition resulted in our patient being submitted to a variety of investigations.

Renal pedicular ligation and stripping is the recommended treatment, although recurrent chyluria may occur in up to 26% of patients (Yu *et al.*, 1978), due either to inadequate stripping of the pedicle or to the presence of a fistula on the contralateral side.

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Self-displacement of a Ureter containing a Stone

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Case Report

A 39-year-old man was admitted with right flank pain accompanied by gross haematuria. A mass occupying the right flank was detectable on physical examination and routine laboratory tests were unremarkable.

A plain film of the abdomen (Fig. 1) showed an area of calcification situated on the left of the lumbar spine, consistent with a stone in the left ureter. A CT scan (Fig. 2) showed a huge right hydronephrosis. The right ureter is shown containing the above-mentioned stone, but situated to the left of the mid-line.

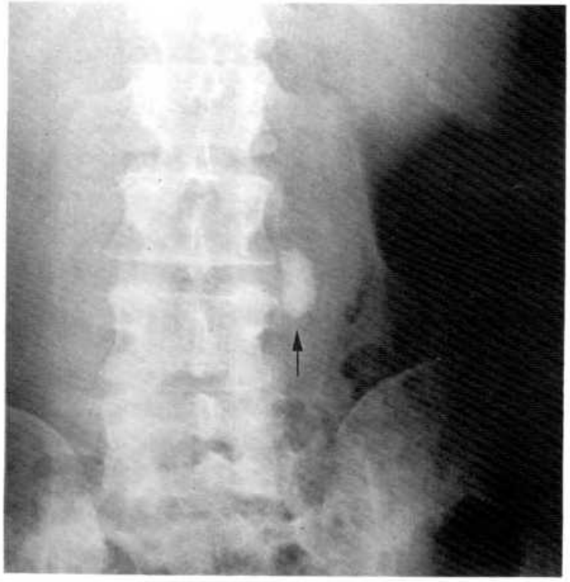

Fig. 1 Plain film of urinary tract shows an area of calcification which appears to lie in the left ureter.

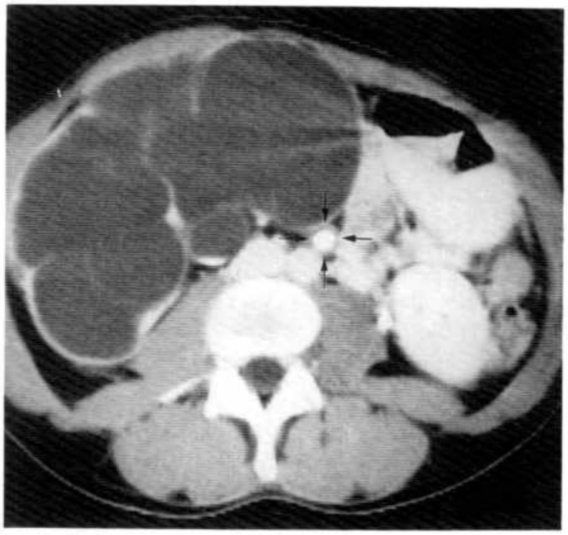

Fig. 2 CT scan of same patient demonstrates large *right* hydronephrosis displacing its ureter containing the stone to the left of the midline.

At operation, the kidney and the proximal ureter above the stone were grossly dilated and contained about 3700 ml of dirty, blood-stained urine. The right kidney was removed together with the upper part of the ureter containing the stone. Pathological examination showed chronic pyelonephritis with parenchymal atrophy. The patient has recovered completely and is in good health 6 months post-operatively.

This case, in which the patient's stone seemed to lie in the contralateral urinary tract, is extremely rare: we have found no similar reports in the current literature.

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Bilateral Testicular Metastases of Pulmonary Small Cell Carcinoma: a Rare Incidental Finding following Orchiectomy for Prostatic Carcinoma

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Case Report

A 77-year-old man was admitted with a well differentiated carcinoma of the prostate, diagnosed by transrectal biopsy. Physical examination revealed no additional abnormalities. Chest X-ray, acid and alkaline phosphatase were within normal limits. Bone scan revealed increased uptake of vertebra C5, thought to be due to degenerative changes. Transurethral resection of the prostate was performed, followed by external beam irradiation.

The patient was readmitted 10 months later with severe nuchal pain radiating to the left forearm. Enzymatic markers remained normal. Bone scan revealed a further increase in uptake of vertebra C5 and osteolytic lesions were seen in X-rays of the cervical spine. Bilateral metastases were seen on the chest film, 2 peripheral and 1 perihilar. Stage D2 carcinoma of the prostate was diagnosed and bilateral orchiectomy performed. After the operation, skeletal pain became progressively more severe.

Pathological examination of the testes showed no gross abnormality except for a small mass in each testis. Histologically, these masses proved to be metastases of undifferentiated small cell carcinoma, probably of pulmonary origin (Fig.). This tumour was quite different from the well differentiated carcinoma found in the prostatic biopsy. The patient died soon after orchiectomy. At autopsy, an undifferentiated small cell carcinoma, 3 cm in diameter, was found in the perihilar region of the left upper lung lobe, with extensive metastatic spread in both lungs and abdominal organs. Ultrastructural examination showed neurosecretory granules in some of the tumour cells.

Comment

Metastatic tumours within the testis are very uncommon and only 15% are bilateral. The most common sites of the primary tumour are prostate, lung, malignant melanoma, colon and kidney, in order of decreasing frequency, and differentiation from a primary tumour of the testis can often be difficult (Peterson, 1986). Price and Mostofi (1957) stated that more than 60% of testicular tumours in patients over the age of 50 are metastatic. The incidental diagnosis of lung cancer by orchiectomy performed for prostatic carcinoma is a rare event.

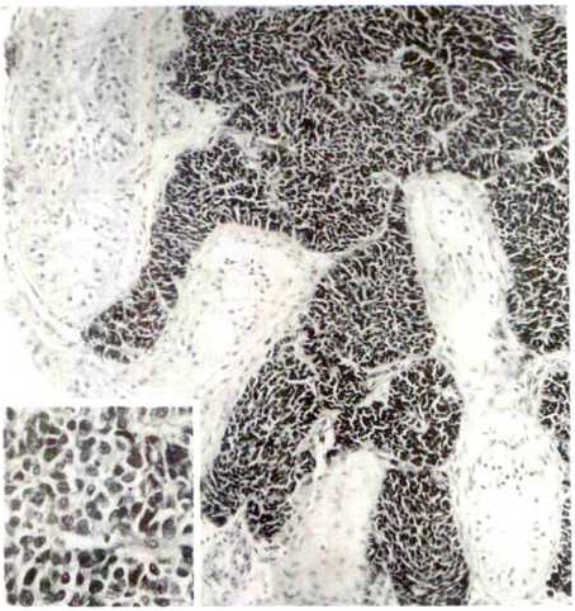

Fig. Testis, interstitial infiltration by metastatic small cell undifferentiated carcinoma. (H and E ×100). Inset: cellular details of tumour. (H and E ×250).

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Ureteric Injury during Laminectomy for a Prolapsed Disc

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Ureteric injuries during lumbar disc surgery are rare and difficult to diagnose (Borski and Smith, 1960; Parker, 1971; Defay *et al.*, 1986).

Case Report

A 53-year-old patient was admitted in August 1985. He had been operated on in June 1985 in the neurosurgical department of another hospital for a prolapsed lumbar disc. This was his second operation for this condition. Post-operatively he had abdominal pain, oliguria, fever, abdominal distension and vomiting. An exploratory laparotomy was done but the cause of his symptoms was not found. The wound healed and the patient was discharged, only to be readmitted 24 h later with a urinoma in the left iliac region; this was immediately incised. Intravenous urography revealed a left hydronephrosis and hydroureter with extravasation (Fig.). Retrograde ureteropyelography showed the inferior segment of the ureter and the pool of contrast already seen on the urogram. Injury to the inferior left ureter was diagnosed. At operation both ureteric stumps were found. An end-to-end anastomosis was impossible because the stumps were too short. The ends of the ureters were incised obliquely; the posterior wall of the ureter was anastomosed with catgut sutures and a splinting catheter was inserted. The post-operative course was uneventful. The splinting catheter was removed 24 days later. The patient passed urine normally and there was no leakage through the wound. He was discharged 10 weeks after the operation. Urography 1 year later showed good function of both kidneys and a normal left ureter.

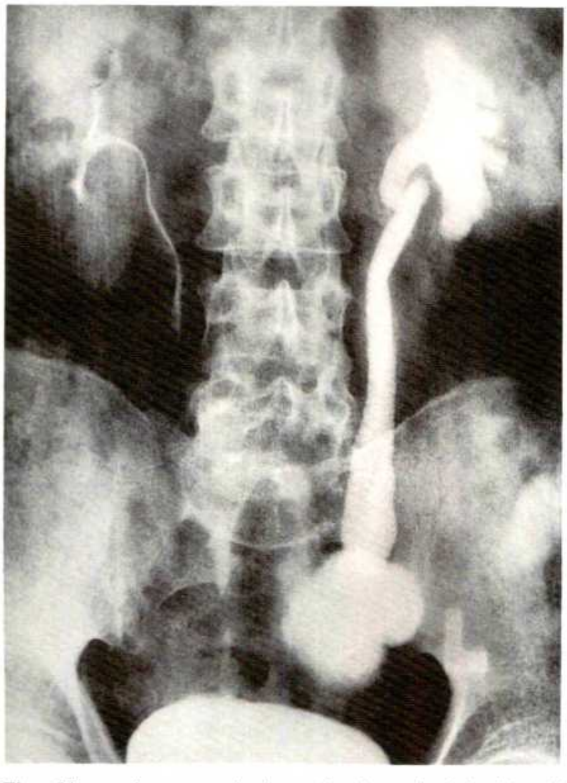

Fig. Urography: ureterohydronephrosis on the left side with extravasation of urine into a pool.

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Triorchidism with Torsion

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Case Report

A previously well 21-year-old man presented with 3 episodes of severe pain in the left testis. Each lasted 3 to 4 h and then spontaneously improved. On examination the right testis, epididymis and cord felt normal. However, on the left the findings were thought to be a small testis and a separate cyst. Ultrasound indicated two similar-sized structures on the left with the same appearance and echo pattern. He was thought to have triorchidism with subacute torsion on the left.

At elective operation 2 small left testes were found connected by a single large epididymis (Fig.). The mesorchium of the upper testis was narrow and readily capable of undergoing torsion. There was a single vas. Upper and lower testicular biopsy confirmed normal spermatogenesis. The left testes and the right testis, which also had a narrow mesorchium, were fixed.

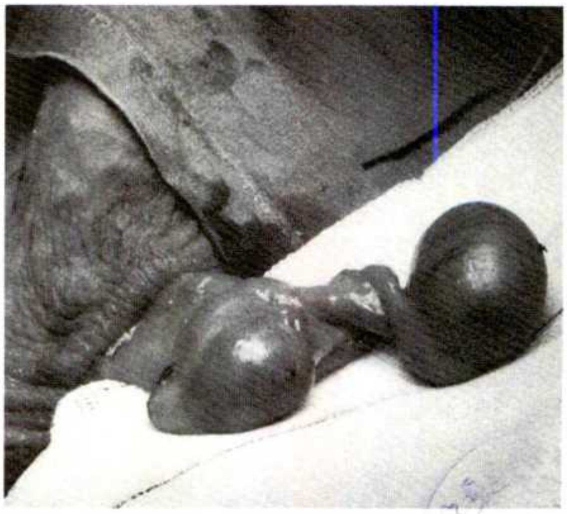

Fig.

Comment

Triorchidism is a rare congenital abnormality. Approximately 70 histologically proven cases have been reported since the first case by Lane in 1895. Only 7 of these were associated with torsion. According to a current theory, in our patient this maldevelopment would have arisen from a transverse division in the upper half of the genital ridge (Nocks, 1978). This type of division produces a supernumary testis prone to torsion.

Most cases of triorchidism occur on the left and associated features include indirect inguinal hernia (30%) and hydrocele (9%) (Pelander *et al.*, 1978). Only 2 cases of cancer in triorchidism have been reported: 1 teratoma and 1 seminoma (Scott, 1980). We consider prophylactic orchiectomy is unnecessary and advise exploration and biopsy with fixation if indicated.

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Points of Technique

Treatment of Urethrovaginal Fistula

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A new method combining polyglycolic acid suture with fibrin adhesive for the treatment of urethrovaginal fistulas is described.

Case Report

A 50-year-old woman with a past history of stress incontinence relieved by anterior colporrhaphy developed an 8 × 8 mm urethrovaginal fistula in the distal third of the urethra. Urethrocystoscopy and cysto-urethrography confirmed the position distal to the sphincter. A biopsy from the fistula area showed chronic inflammation. After circumcising the fistula, the urethral epithelium was closed with interrupted 3/0 polyglycolic acid sutures. Before the sutures were tied, however, fibrin adhesive (Beriplast) was injected between them. The vaginal mucosa was sutured in the same way and finally the two suture lines were sealed with fibrin adhesive. The indwelling catheter was removed after 10 days, when the fistula had healed. No relapse has occurred over a follow-up period of 6 months.

Fibrin adhesive has been available for a decade and is used for performing intestinal anastomoses (Hjortrup *et al.*, 1986; Kjærgaard *et al.*, 1987), for closing intestinal fistulae and for reducing bleeding following transurethral resection of the prostate (Luke *et al.*, 1986). Fibrin adhesive has two components, fibrinogen concentrate and thrombin. Fibrin gluing mimics the last step in blood clotting. Thrombin is the solidifier of the system and causes the fibrin to coagulate. Factor XIII is added as an adjuvant and aprotinin is also added to prevent early disruption of the clot by fibrinolysis.

The two components of the adhesive are stored in separate syringes attached to the inlets of a double tube dispenser following addition of the adjuvants. The components are brought together and applied with a needle attached to the dispenser outlet. Solidification of the clot occurs within 10 to 20 s after mixing and a new needle has to be used for each application. A total amount of 1 ml was used.

Instead of sealing the sutures with glue, we inject the glue between the sutures before they are tied. In that way the risks of haemorrhage, necrosis and infection are reduced and these are the major reasons for the recurrence of fistulae.

References

Hjortrup, A., Nordkild, P., Kjaergaard, J. *et al.* (1986). Fibrin adhesive versus sutured anastomosis. a comparative intra-individual study in the small intestine of pigs *Br J. Surg.*, 73, 760–761

Kjaergaard, J., Nordkild, P., Sjøntoft, E. *et al.* (1987). Non-sutured fibrin adhesive vs. sutured anastomosis. A comparative intra-individual study in the dog colon. *Acta Chir Scand*, **153**, 599–601.

Luke, M., Kvist, E., Andersen, F. *et al.* (1986). Reduction of post-operative bleeding after transurethral resection of the prostate by local instillation of fibrin adhesive (Beriplast) *Br J Urol.*, **58**, 672–675

Requests for reprints to: J. Krogh, Department of Urology D, Bispebjerg Hospital, DK-2400 Copenhaven NV, Denmark.

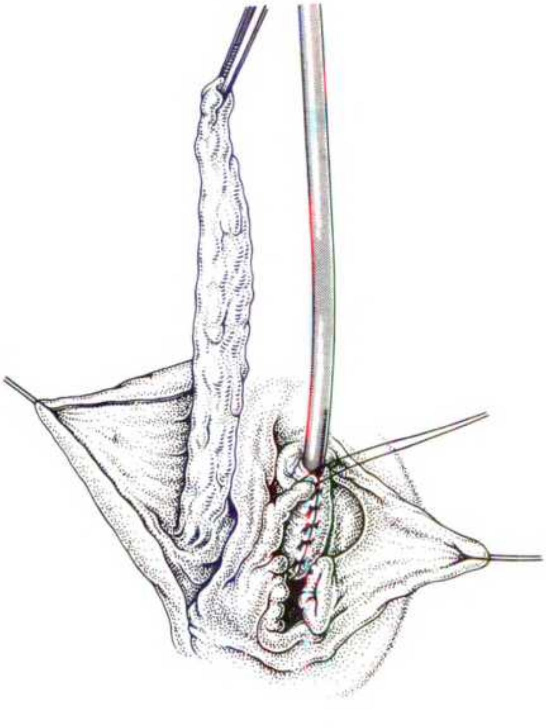
Urethral Salvage Following Erosion of an Artificial Sphincter Cuff in Female Patients

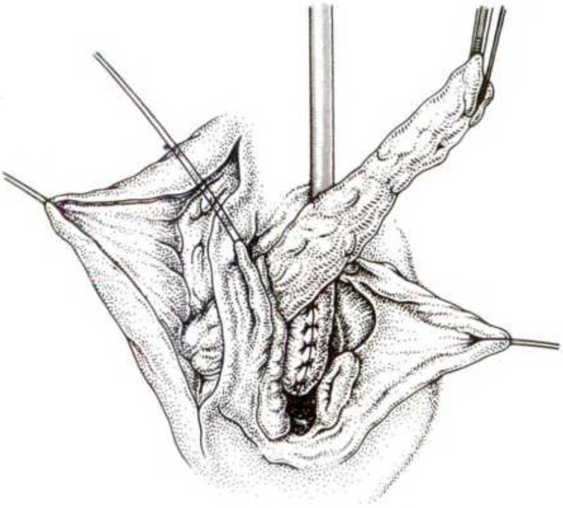
G. GILLON, H. A. P BOUCAUT and A. R MUNDY, *Department of Urology, Guy's Hospital, London*

Erosion of the cuff into the vagina or urethra is a recognised complication of an artificial urinary sphincter (AUS) and when it occurs, sooner or later, the cuff (if not the whole device) must be removed.

It was previously our practice in such a situation to remove the cuff transabdominally and then to mobilise the omentum and wrap it around the urethra to encourage healing and, more importantly, to preserve the tissue plane for subsequent insertion of another device. More recently we have developed a different technique, equally effective for the salvage of the female urethra.

Our current practice is to use unilateral or bilateral pedicled labial fat pads depending on the size of the fat pad. A vertical incision is made along the edge of the labium majus. The fat pad is identified and dissected upwards as far as the external inguinal ring and downwards to the level of the posterior fourchette, where its vascular pedicle enters. The length of the pedicled flap is 8 to 12 cms (Fig. 1). The AUS cuff is removed through





another incision in the anterior vaginal wall or, if that is the problem, through the site of the vaginal erosion. The other components of the AUS are removed through the groin. The pedicled fat pad flaps are then tunnelled through to the vaginal incision and wrapped around the urethra (Fig. 2). A urethral catheter is left in for 1 to 3 weeks, depending on whether it is a vaginal or urethral erosion.

The technique has the advantage that it avoids a major abdominal procedure and requires a shorter hospital stay. It is nonetheless equally effective in achieving its objectives.

We recommend this technique for the salvage of the female urethra when AUS cuff erosion occurs.

Requests for reprints to: A. R. Mundy, Department of Urology, Guy's Hospital, St Thomas Street, London SE1 9RT.

British Journal of Urology (1989), **63**, 557–558

Notices

British Association of Urological Surgeons

President: R. T. Turner-Warwick, DSc, DM, MCh, FRCP, FRCS, FACS

Annual Meeting: St Helier, Jersey, Channel Islands. 20–23 June 1989

All correspondence to: Hugh N. Whitfield, MChir, FRCS, Honorary Secretary, British Association of Urological Surgeons, Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN.

C.-E. Alken Prize

An endowment fund has been established to further clinical work and research in the field of Urology by presenting an annual award of SwF 10,000 for outstanding scientific endeavours. The award will be for an unpublished work in the field of Urology. An award certificate will also be presented. The prize money may be divided among several contributors.

The papers may be written in either German or English and three copies must be submitted by 30 September 1989 to: Stiftungsrat C.-E. Alken-Stiftung, Advokaturbüro Dr F. Kellerhals, Bundesplatz 4, CH-3011 Bern, Switzerland.

Each submission must be affixed with a code word and must not bear the author's name. In addition, a sealed envelope labelled with the code word is to be included, containing on a separate sheet of paper the author's name and professional standing, together with the code word.

The adjudicators for the award will be the Board of Directors of the endowment fund and their decision will be final.

Shackman Travelling Fellowship 1990

Applications are invited from Medical Practitioners registered in the United Kingdom who are Senior Registrars in an accredited training programme in urology or Consultant Urological Surgeons of no more than 5 years' duration. Applicants of equivalent university status will also be considered.

The Fellowships are intended to provide sufficient support to enable the holder to undertake a period of study, either in the United Kingdom or abroad, for a period of not less than 6 weeks.

The subject to be studied must be related either to urology or to renal transplantation and may be either a laboratory or a clinical investigation.

The closing date for applications is 1 September 1989.

Further particulars from and all correspondence to: Taylors, Solicitors, 119 High Street, Newmarket CB8 9AG.

Edinburgh Urological Festival

A Joint Postgraduate Urological Meeting: Edinburgh University Department of Surgery (WGH) and Department of Urology, University of California, Davis

Edinburgh. 23–26 August 1989

The programme will consist of review lectures by invited speakers from the USA and Europe, with short papers by participants on the following topics: Superficial Bladder Cancer; Bladder Dysfunction; Reconstructive Surgery; Infertility and Sexual Dysfunction; Neo-adjuvant Chemotherapy; Flow Cytometry in Urology.

Further particulars from: Urological Festival Secretary, University Department of Surgery (WGH), Western General Hospital, Crewe Road, Edinburgh EH4 2XU, UK *or* Professor A. Stone, Department of Urology, University of California, Davis, Sacramento, USA.

54th Congress of the Belgian Society of Urology

Brussels, Belgium. 27–28 May 1989

The topic will be "Lower Urinary and Genital Pathology in Children."

Further particulars from: Dr F. F. Wart, C.H.U.-I.M.C.A.G., Division of Urology, Boulevard Zoe Drion 1, B-6000 Charleroi, Belgium.

Congress of the Spanish Association of Urology

Toledo, Spain. 28–31 May 1989

Further information from: REYCOSA, Parque de la Colina, 6, bajo dcha, 28043 Madrid, Spain.

XXVIth Congress of the European Dialysis and Transplant Association—European Renal Association

Göteborg, Sweden. 11–15 June 1989

Further information from: General and Scientific Secretariat, Transplant Unit, Department of Surgery, Sahlgrenska Hospital, S-413 45 Göteborg, Sweden.

S.U.W.O. (Urological Research Foundation) Symposium on Paediatric Urology

Rotterdam, The Netherlands, 30 June and 1 July 1989

The following topics will be discussed: ureteric obstruction, duplication of kidney and ureter, neurogenic bladder dysfunction, anorectal malformation and vesicoureteric reflux.

Further information from: Mrs S. Wolff, Department of Urology, University Hospital Dijkzigt, Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands.

Second Copenhagen Symposium on Uroradiology

Herlev, Denmark. 27–30 August 1990

The following topics will be included: Upper urinary tract imaging and intervention; Contrast medium nephrotoxicity; Hydronephrosis/obstruction; The urinary bladder; Genital radiology; The adrenal glands; Free communications.

Further information from: H. S. Thomsen, Department of Diagnostic Radiology 54E2, Herlev Hospital, DK-2730 Herlev, Denmark.

Annual Meeting of the Swiss Society of Urology

Aarau, Switzerland. 21–23 September 1989

The main themes will be Renal Carcinoma and Ultrasound in Urology.

Further information from: Professor R. Tscholl, Urologische Klinik, Kantonsspital, CH-5001 Aarau, Switzerland, or Professor D. Hauri, Urologische Klinik, Universitätsspital, CH-8091 Zürich, Switzerland.

Fourth Steglitz Pediatric Surgical Symposium: Laser Application in Children

Berlin, West Germany. 10 and 11 November 1989

Further information from: Dr Felix Schier, Department of Pediatric Surgery, Free University of Berlin, Hindenburgdamm 30, 1000 Berlin 45, West Germany.

Archivos Españoles de Urologia

Readers are advised that the above journal now has a new publisher. To ensure that subscribers continue to receive their copies of the journal they are requested to contact Ediciones BOK, S.A., Pilar Millan Astray, 4, esc. 2, 1.°A, 28009 Madrid, Spain.

British Journal of Urology (1989), 63, 559
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Book Reviews

Disorders of Male Sexual Function. Edited by D. K. Montague. Pp. x+264. Chicago, London, Boca Raton: Year Book Medical Publishers. 1988. Price £40.50.

Pharmacologically induced erections have stimulated considerable interest in the management of sexual problems by the urologist. However, as is emphasised in this book, the modern assessment and treatment demands a many faceted approach to the problem, often best achieved within the context of a team of interested individuals with particular skills to offer.

For this type of publication to be particularly useful to those practising outwith a specialised clinic, the authors might have done well to have offered a flow diagram of their own practice on which to base discussion. The first half of the book provides a welcome overview of the investigative techniques currently in use (not thermal thresholds, however). It is only proper that suitable emphasis has been given to the psychological aspects of the problem that are in danger of being neglected as management gets more technologically based and invasive.

In andrology texts there has often been rather too much space devoted to prosthetic surgery at the expense of other approaches. In the second half of this book the authors have avoided this, although venous surgery is poorly covered. The role of intracavernosal injection for those with mainly psychological problems would also have merited more discussion.

This book is recommended for covering the recent advances without disregarding the less than novel.

The Physiology of the Lower Urinary Tract. Edited by M. Torrens and J. F. B. Morrison. Pp. viii+355. London, Berlin, Heidelberg, New York, Paris, Tokyo: Springer-Verlag. 1987. Price £89.00.

This book covers the physiology of the lower urinary tract in great depth and successfully integrates neurophysiological theory with clinical and urodynamic practice. The book is arranged in three broad sections. The first section, entitled Neuromorphology, has contributions from John Dixon, John Gosling and Ahmad Elbadawi. These authors provide a balanced assessment of the morphology of the human and various animal urinary tracts. Comparative neuromorphology is important because much of the data in this field are derived from animal experimentation and extrapolated to the human condition. The second section, on sensory and motor control, has an important contribution from Alison Brading on smooth muscle physiology; the rest of the section is written by John Morrison. The final section, Clinical Physiology, contains an important chapter on neurophysiological measurement by Clare Fowler and Chris Fowler, providing the balance to the well written sections on Urodynamics and Human Physiology by Michael Torrens.

This book is extremely well written. The use of summaries with each sub-section is valuable, especially in the discussion of the central control mechanisms. The chapters are extensively referenced. There is some repetition of theory in the text and there is no discussion of the comparative morphology of the mini-pig, which has been used extensively in the UK as an experimental animal. These minor criticisms apart, this book is essential reading for the urodynamically minded and fills an important gap in the general urological literature

Continence and Incontinence. Psychological Approaches to Development and Treatment. By P. S. Smith and Linda J. Smith. Pp. 280. London, Sydney: Croom Helm. 1987. Price £22.50.

Everyone who looks after patients with urinary incontinence has his or her own approach to the psychological aspects of the condition, and some will admit to being in need of guidance in this field. The aim of this book has been to provide a comprehensive discussion of the behavioural, psychological and developmental background to incontinence and it includes chapters on the history of incontinence, the development of continence and toilet training, nocturnal enuresis and encopresis.

The result is an exhaustive, though somewhat exhausting, academic review of these subjects. One chapter alone offers practical guidelines in bladder training, which are valuable. However, there is a recurrent tendency to discuss the behavioural approach to treatment without considering different physiological types of incontinence. Thus the authors' advice can be somewhat misleading. For instance, fluid restriction is broadly condemned as a form of management. Their reasoning for this is sound whilst considering the training of youngsters with nocturnal enuresis, but would be quite incorrect if applied to older patients with detrusor instability.

In general, although this is undoubtedly a work of scholarship, it lacks the didactic approach which most clinicians and continence advisers need. There is a risk that it will remain unread by the majority of people who, otherwise, might benefit from the experience of these two authors.

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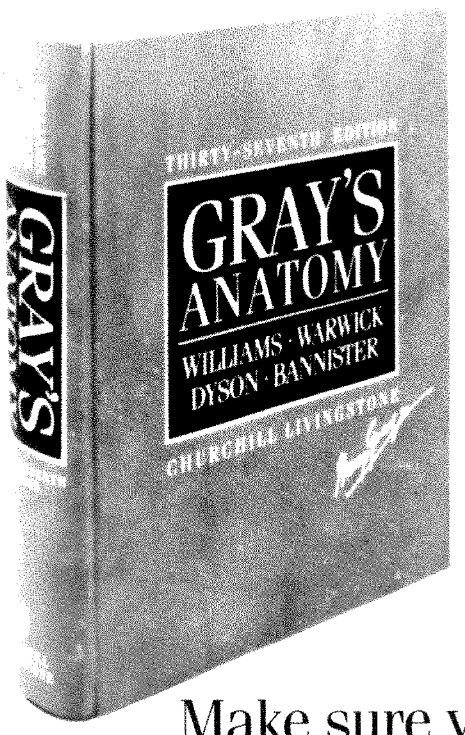

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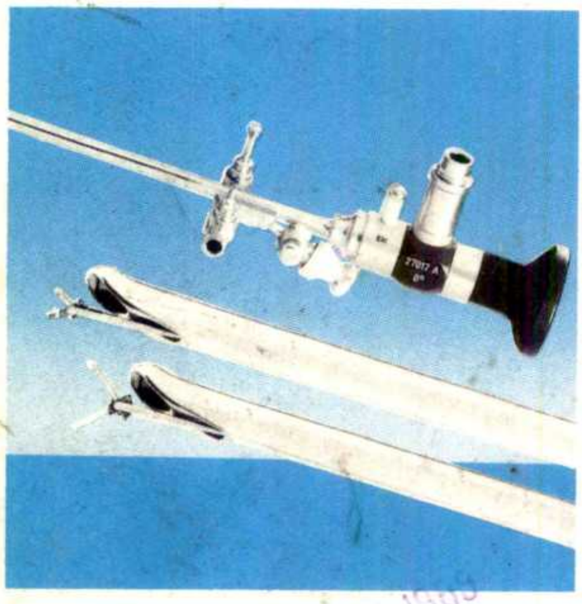

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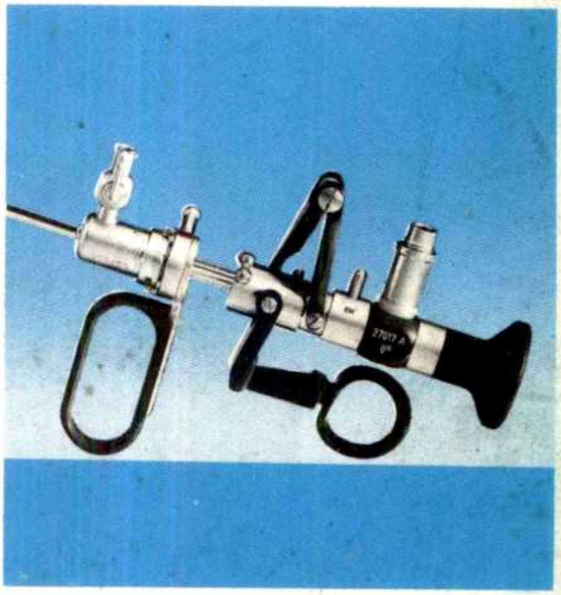

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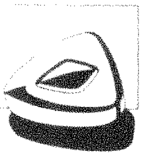

ferences: 1 Iacovou JW, Dunn M. Br J Urol 1987; 60: 526-8. **2** Gower R, Wells P. Neurourol Urodyn 1988; 7: 216-7. **3** Stott MA, Abrams P. Neurourol
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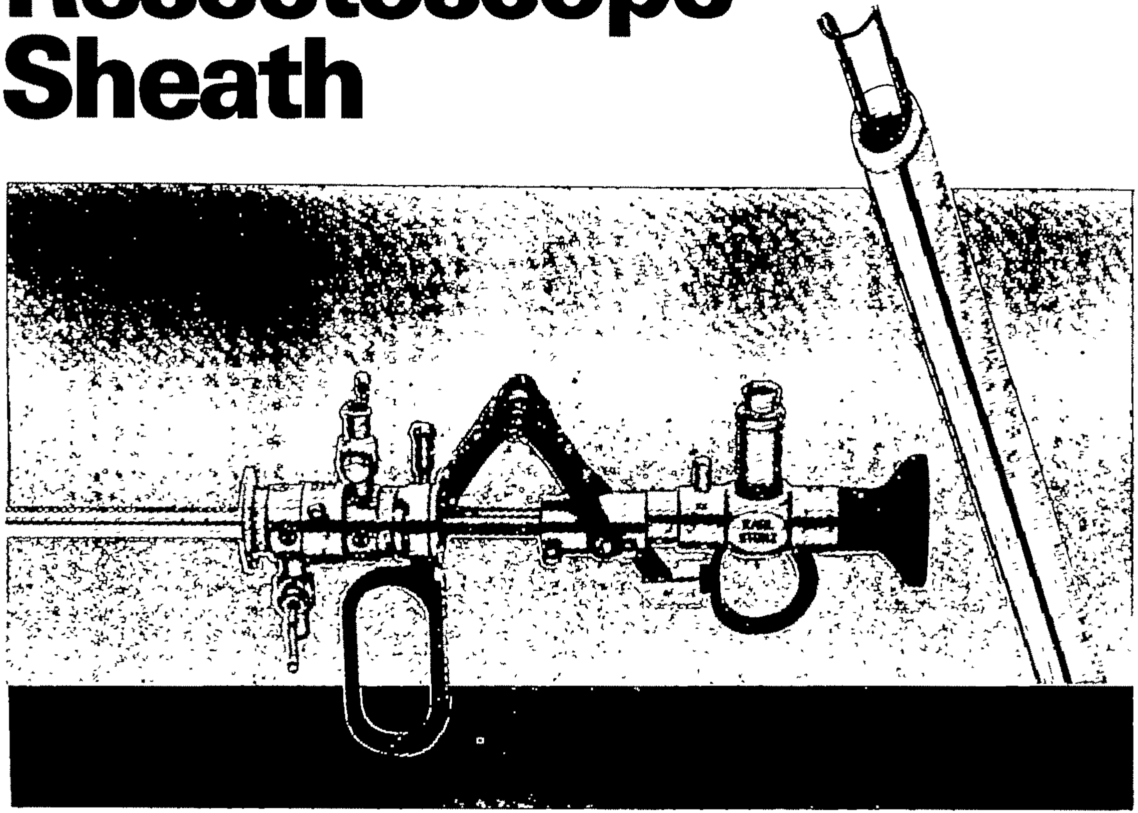

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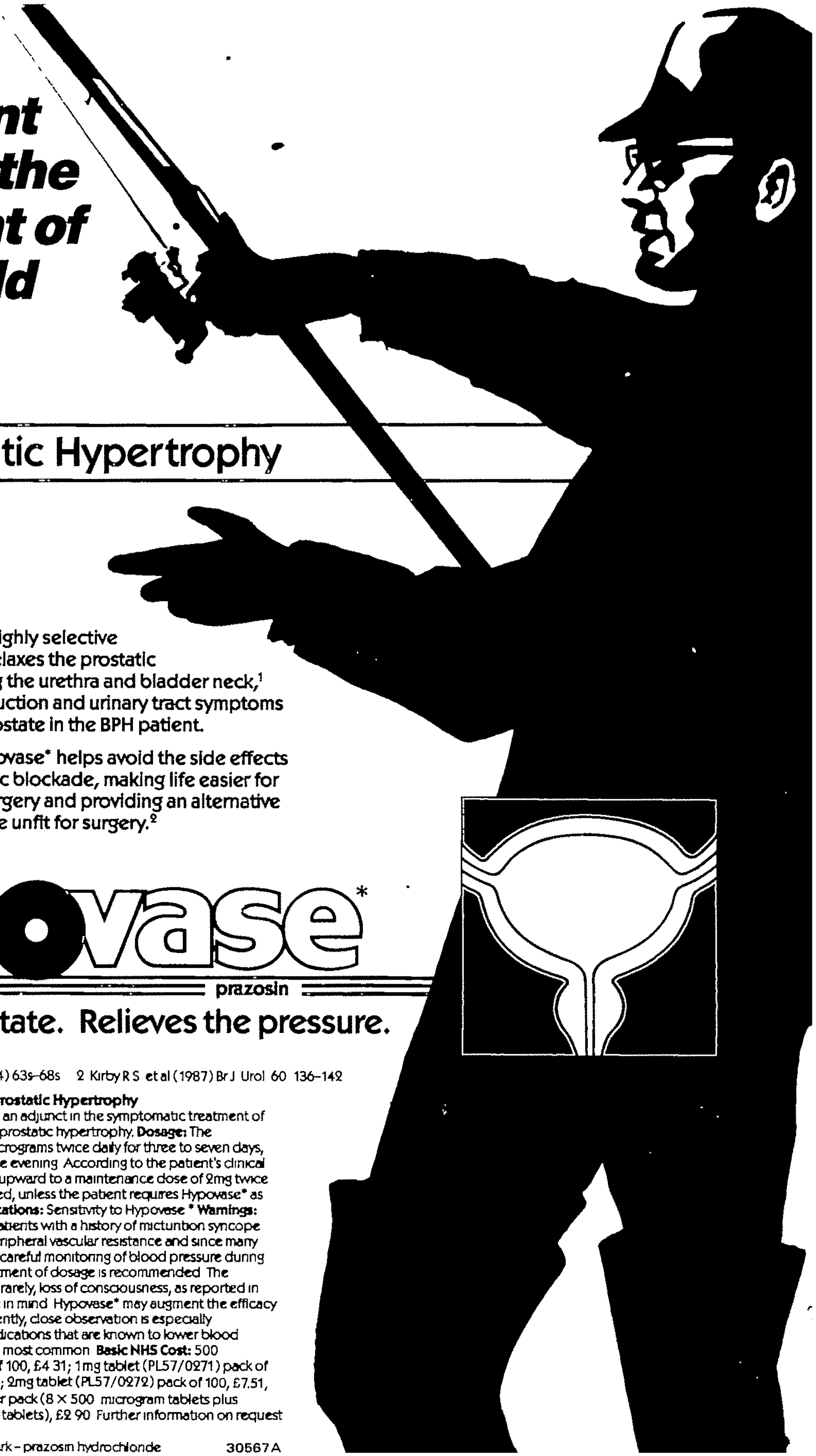

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Hypovase*

prazosin

Relaxes the prostate. Relieves the pressure.

Reference

1. Caine M (1986) Clin Sci 70 (Suppl. 14) 63s–68s 2 Kirby R S et al (1987) Br J Urol 60 136–142

Prescribing Information in Benign Prostatic Hypertrophy

Indications: Hypovase* is indicated as an adjunct in the symptomatic treatment of urinary obstruction caused by benign prostatic hypertrophy. **Dosage:** The recommended starting dose is 500 micrograms twice daily for three to seven days, with the initial dose administered in the evening According to the patient's clinical response, the dosage may be titrated upward to a maintenance dose of 2mg twice daily. This dose should not be exceeded, unless the patient requires Hypovase* as antihypertensive therapy. **Contra-Indications:** Sensitivity to Hypovase * **Warnings:** Hypovase* is not recommended for patients with a history of micturition syncope **Precautions:** Hypovase* decreases peripheral vascular resistance and since many patients with this disorder are elderly, careful monitoring of blood pressure during initial administration and during adjustment of dosage is recommended The possibility of postural hypotension, or rarely, loss of consciousness, as reported in other patient groups should be borne in mind Hypovase* may augment the efficacy of antihypertensive therapy, consequently, close observation is especially recommended for patients taking medications that are known to lower blood pressure **Side-Effects:** Dizziness is the most common **Basic NHS Cost:** 500 microgram tablet (PL57/0270) pack of 100, £4 31; 1mg tablet (PL57/0271) pack of 100, £5 53; 2mg tablet (PL57/0272) pack of 100, £7.51, b d. starter pack (8 × 500 microgram tablets plus 32 × 1mg tablets), £2 90 Further information on request

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British Journal of Urology

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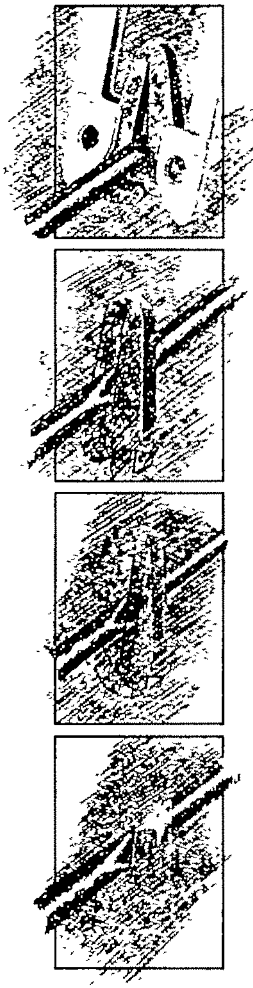

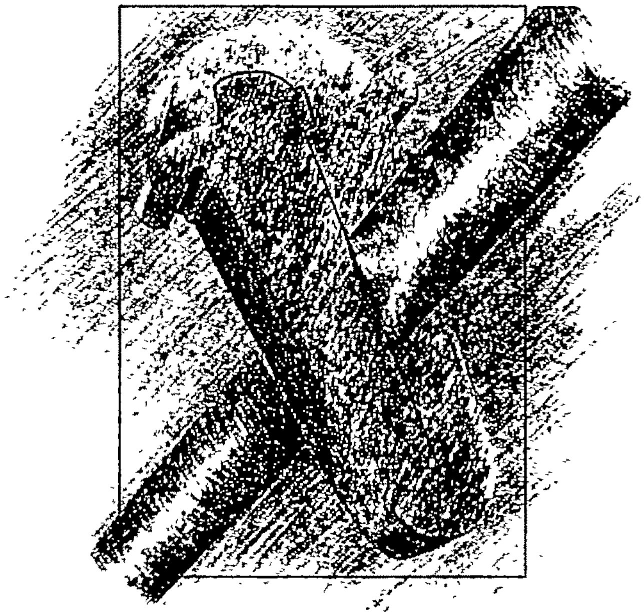

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TECHNICAL DATA

ABSOLOK* EXTRA ▼
STERILE POLYDIOXANONE ABSORBABLE LIGATING CLIPS

Presentation: ABSOLOK Extra Ligating Clips are absorbable, 'V' shaped ligating clips available in four sizes, prepared from the polyester (p-dioxanone) The empirical molecular formula of the polymer is $(C_4H_6O_3)n$ ABSOLOK Extra (polydioxanone) clips are dyed with D & C Violet No 2 during polymerisation Sterilisation is by ethylene oxide gas

ABSOLOK (Polydioxanone) clips are relatively inert, non-antigenic, non-pyrogenic and elicit only a mild tissue reaction during absorption

Action The absorption characteristics of polydioxanone have been extensively studied The general mechanism by which in vivo degradation of polydioxanone occurs is hydrolysis The in vivo hydrolysis of polydioxanone cleaves the ester linkages and initially results in the loss of strength Ultimately, the hydrolysed polymer is eliminated from the body, primarily in urine

The results of implantation studies of polydioxanone clips in animals indicate that the clips retained their strength longer than necessary for a thrombus or clot to occur in a vessel

Data obtained from implantation studies in rats indicate that the absorption of these clips is minimal until about the 90th post-implantation day Absorption is essentially complete within 210 days

Uses: ABSOLOK Extra clips are intended for use as absorbable ligatures These clips are designed to offer a rapid, efficient means of ligation Unlike cautery, the vessel and/or tissue is occluded with no thermal destruction Unlike conventional metallic haemostatic clips, the absorbable clips are radiotransparent Therefore, they will not interfere with interpretations of postoperative X-ray, CT or NMR scans

The ABSOLOK Extra clip applier, designed for use specifically with ABSOLOK Extra clips optimises visibility of the clip at the ligation site and facilitates access to virtually all vessels and/or tissues

Dosage and Administration: By implantation

Contraindications, Warnings Etc: ABSOLOK Extra clips should not be used where prolonged or permanent ligation of tissues or vessels is required

The use of the ABSOLOK Extra clip in vasectomy procedures and tubal ligation procedures is contraindicated The safety and effectiveness of the ABSOLOK Extra clip in contact with neural tissues have not been established

Use only with an ABSOLOK Extra clip applier of the appropriate size Identification for each size is facilitated by the matching colour on the clip cartridge and the handle of the applier

The clip must be latched to ensure proper ligation of the vessel or tissue

Tissue must be compliant enough to allow latch to engage securely Depending on the toughness of the surrounding tissue, the latch may not displace the tissue enough to latch Some dissection of tissue from vessel surface may then be necessary

As with any ligating device, the surgeon should inspect the ligation site following placement of the clip to ensure proper haemostasis and ligation has been achieved

Do not re-sterilise the clips or clip cartridge

Pharmaceutical Precautions: The recommended storage conditions are below 25°C, away from moisture and direct heat Shelf life is 5 years, the expiry date is shown on each pack

Legal Category: Not Applicable

Package Quantities: Clips are available in four sizes as follows

Product Code	**Colour Coding**	**Approximate Vessel Sizes**
AP100	Blue	0 5-2 0mm
AP200	White (silver handle on applier)	1 5-3 0mm
AP300	Green	2 5-4 0mm
AP400	Yellow	3 5-5 5mm

Each colour coded cartridge contains ten clips Each cartridge is sealed in an aluminium foil pack and peel apart overwrap pouch The sales unit is a filmwrapped box containing 6 packs

Further Information: No clip related adverse reactions were reported during clinical trials

Based upon the experience of the surgeon, ABSOLOK Extra ligating clips sizes and corresponding applier selection should be consistent with the vessel being ligated

Closed clips have minimal gap ensuring even the smallest vessels in the appropriate size range will be properly ligated

The latch of ABSOLOK Extra clips is designed to allow direct application to vessels with little or no tissue dissection

PL 0508/0015

Reference Papers: ABSOLOK POLYDIOXANONE ABSORBABLE LIGATING CLIPS FOR SURGICAL LIGATION

'Polydioxanone in Cardiovascular Surgery'
Thorac Cardiovasc Surgeon 32 (1984) 100-101
P T Harjola, K Ala-Kulju and L Heikkinen

'A New Absorbable Ligating Clip for use in Cholecystectomy' Journal of Royal College of Surgeons of Edinburgh January 1984 Volume 29 Number 1
A Allan, M J Cooper, D J Leaper

'Surgical Ligation Clip Artifacts on CT Scans' Radiology 1985 (USA) 156 831-832 Steven C Gross, John B Kowalksi, Seung-HO H Lee, Bernard Terry and Steven J Homickman

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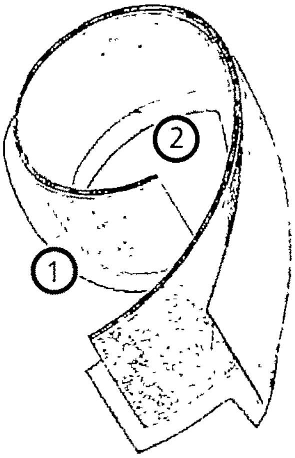

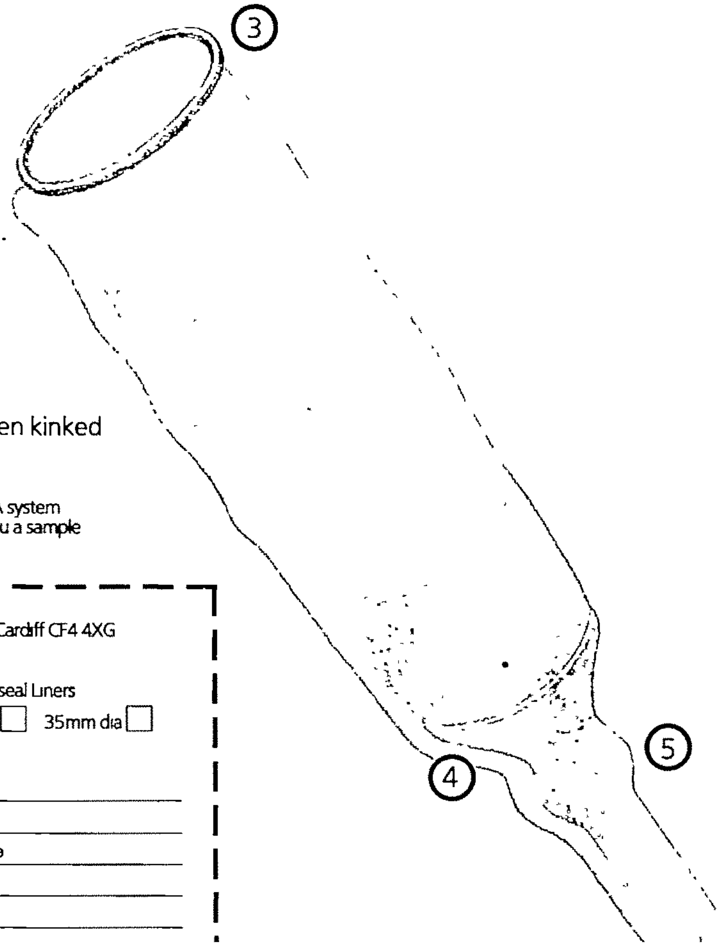

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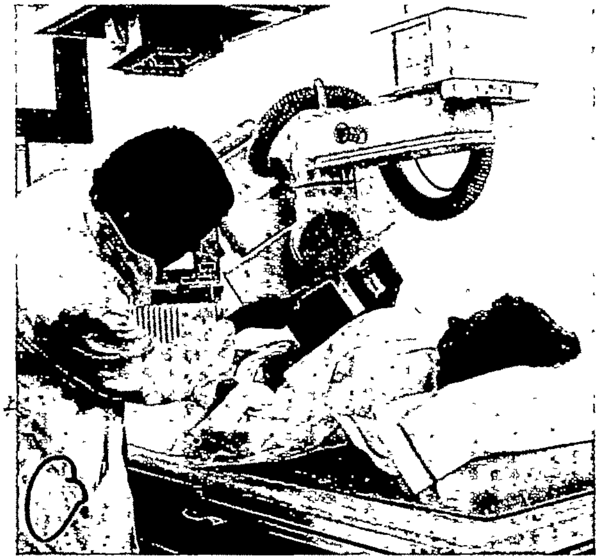

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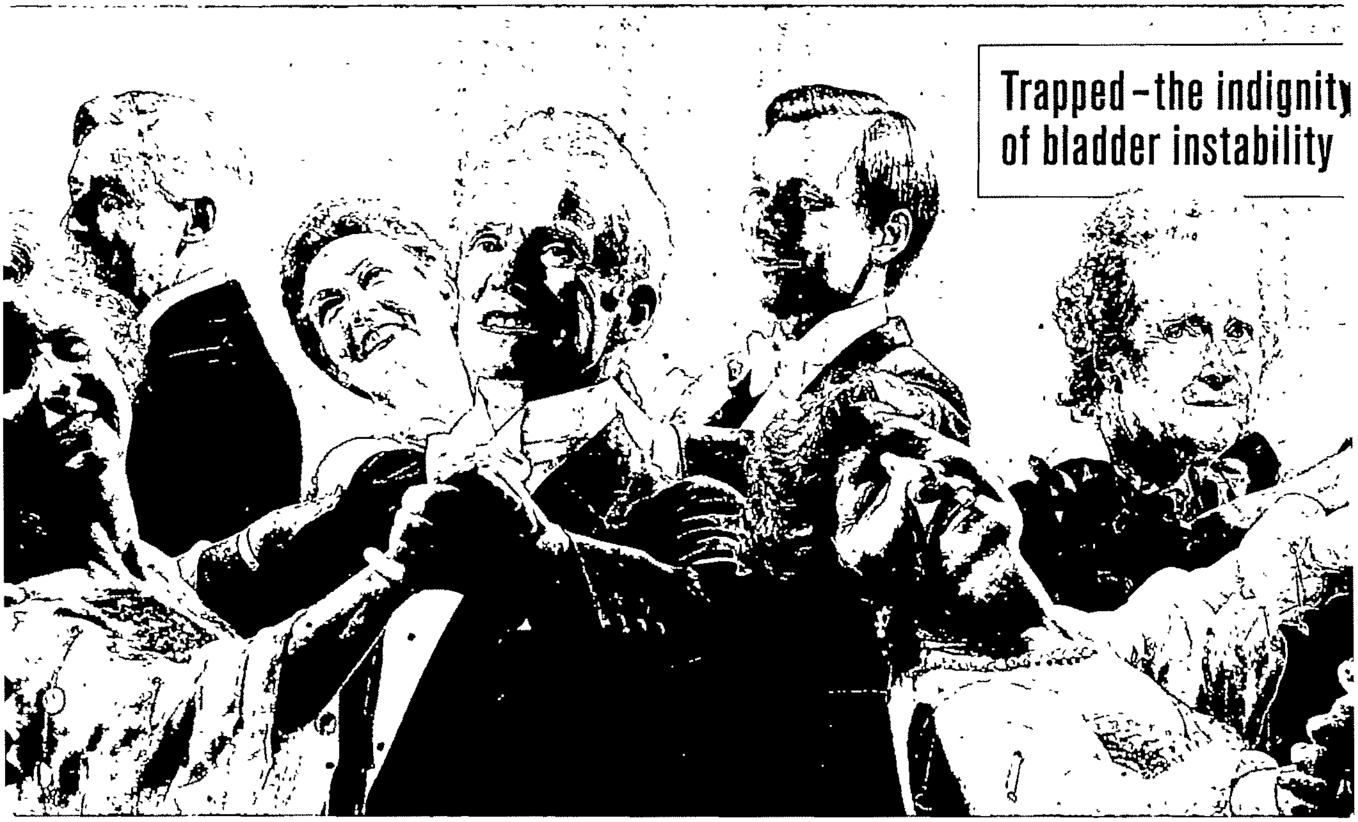
Topics to be discussed include: *state of the art bladder cancer screening, innovative approaches, feasibility of a clinical screening trial*, and *recommendations for high risk groups.*

Invited and contributed papers will be presented during the two-day meeting. The proceedings will be published in the *Journal of Occupational Medicine.*

ABSTRACTS of no more than 500 words should be submitted no later than **JULY 15, 1989** to .

Dr Paul Schulte
Chief, Screening & Notification Activity
National Institute for Occupational Safety & Health (NIOSH)
R–13, 4676 Columbia Parkway, Cincinnati, Ohio 45226, USA

For further information contact Dr Schulte in USA on **(513) 841 4207**



Micturin™ (terodiline) ▼ **Abbreviated prescribing information Presentation** White film coated tablets containing terodiline hydrochloride 12 5mg **Indications** Urinary frequency urgency and incontinence in patients with detrusor instability (motor urge incontinence) and neurogenic bladder disorders eg uninhibited bladder and reflex bladder disease **Usage** Adults 1 2 tablets twice daily The final dose will depend upon response and/or tolerance to side effects It will not normally be necessary to exceed one tablet twice daily in the frail elderly patient It is recommended that treatment should be continued for 2-3 weeks so that the optimal response is obtained Children Not

recommended **Contra-indications** Micturin is contra indicated in the following groups of patients those with bladder outflow obstru
flaccid bladder or high residual urine obstructive lesions particularly of the upper gastrointestinal tract severe hepatic dysfunction or
tract dysfunction glaucoma **Precautions** As with other drugs with anticholinergic effects caution should be observed in patients with
retention incipient obstruction of the gastrointestinal tract fever thyrotoxicosis or those with heart disease where an increase in heart
undesirable Caution should also be observed in patients with hepatic dysfunction and in the frail elderly patient Potentiation of

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The next Intercollegiate Specialty Examination in Urology will be held in the **London Hospital, Whitechapel, London, on Friday 22 September 1989.**

Candidates will be required to hold the Surgical Fellowship of one of the Royal Colleges of Surgeons of Great Britain or Ireland and to have completed a period of post-Fellowship training in posts approved by the Intercollegiate Board in Urology of not less than four years, as follows :

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(b) Three years in Clinical Urology in posts approved by the Specialist Advisory Committee in Urology. At least one year of this period must be at the Senior Registrar level.

The regulations and application form may be obtained from the Secretariat, INTERCOLLEGIATE SPECIALTY BOARDS, 10 Hill Square, Edinburgh EH8 9DR.

Completed applications for entry must be received by **Friday, 4 August 1989**

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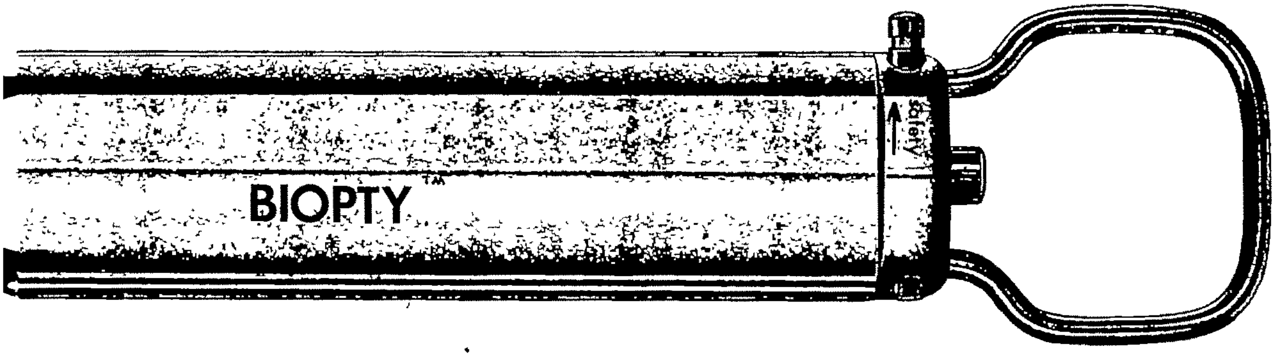

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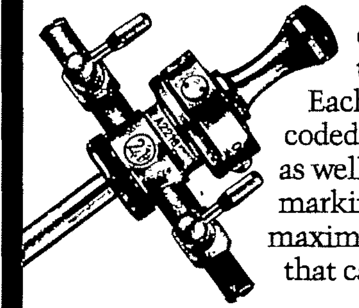
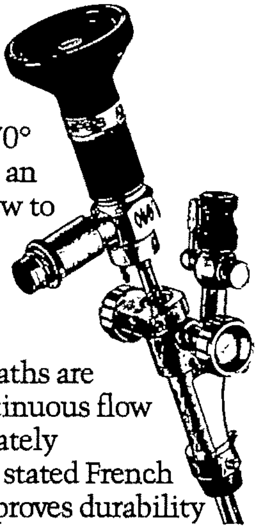
The Olympus OES range of lower tract urological telescopes features high resolution lens systems which give large, bright, evenly illuminated images for accurate diagnosis and treatment of urological disorders.

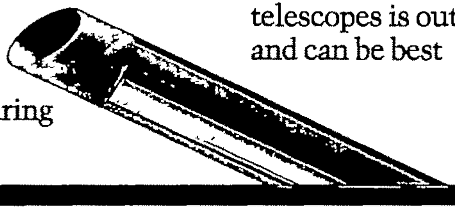
For rigid cystoscopy, the 70° telescope can be used with a range of cystoscope sheaths, constructed of a high quality German silver to improve durability. Each sheath size is colour coded for easy identification as well as incorporating markings to show the maximum accessory size that can be used.



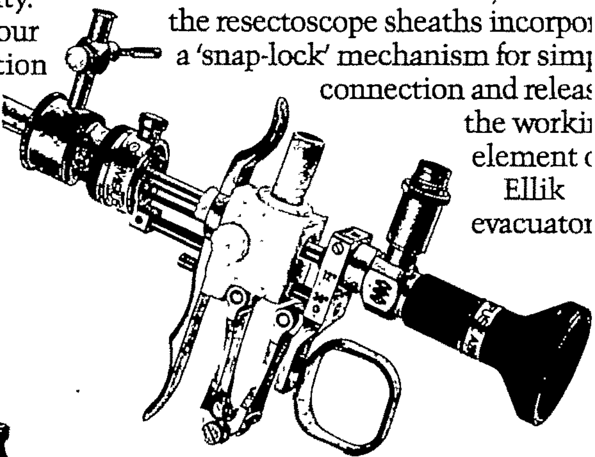
Single or double Albarran mechanisms are available, enabling direct connection of the 70° telescope, which features an ultra-wide 90° field of view to allow inspection of the bladder with minimal manipulation.



The resectoscope sheaths are available in single or continuous flow versions and all are accurately manufactured to the true stated French sizes. A ceramic beak improves durability and ensures electrical safety whilst each single flow sheath incorporates a rotating water collar, to minimise the possibility of disruption of fluid flow during the procedure.

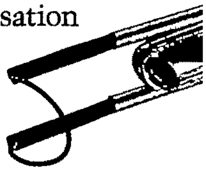


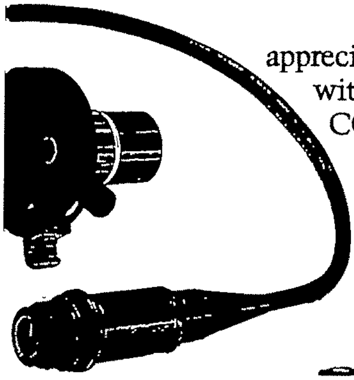
To facilitate bladder evacuation, the resectoscope sheaths incorpo a 'snap-lock' mechanism for sim connection and releas the worki element Ellik evacuato



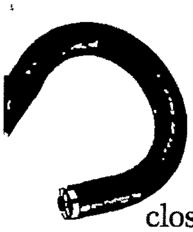
When the complete system is assembled, fine balance and attention to detail makes Olympus system comfortable to use.

The resectoscope can be used with 12 30° telescopes and a variety of loops is available to enable optimisation of the angle of cut. The quality and clarity of image through the telescopes is outstanding and can be best

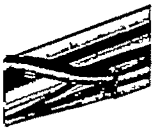




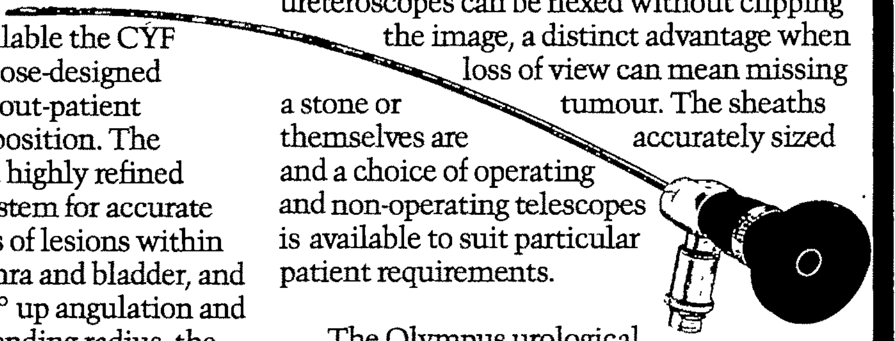
appreciated when used with specialised CCTV equipment such as the Olympus OTV-S2 endoscopic TV camera.



..Olympus also has available the CYF exible cystoscope, a purpose-designed ıstrument which makes out-patient ⁄stoscopy a practical proposition. The ıstrument incorporates a highly refined optical system for accurate diagnosis of lesions within the urethra and bladder, and with 210° up angulation and a large bending radius, the CYF is ideally suited for close-up and complete inspection f the bladder mucosa. The insertion tube has ur stages of flexibility, to optimise patient omfort and ease introduction. With a rigid cope style eyepiece, the CYF is lso compatible with existing CTV, photographic or other aching equipment and the ıstrument is of course unconditionally guaranteed for one year by KeyMed.

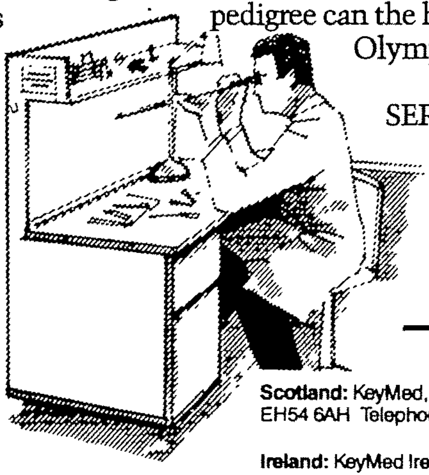


The range of upper tract equipment is equally impressive — the percutaneous nephroscopes are both versatile and easy to use. With the Olympus system, you can choose between the use of continuous flow, Amplatz, or even fiberoptic nephroscopy for inspection of the complete collecting system.



For ureteric inspection, the Olympus ureteroscopes can be flexed without clipping the image, a distinct advantage when loss of view can mean missing a stone or tumour. The sheaths themselves are accurately sized and a choice of operating and non-operating telescopes is available to suit particular patient requirements.

The Olympus urological endoscopy system is the result of many years' development, utilising the expertise accumulated during 70 years at the forefront of technology in both optics and instrument mechanics. Only with such a distinguished pedigree can the highest quality be expected. Olympus meets this expectation.



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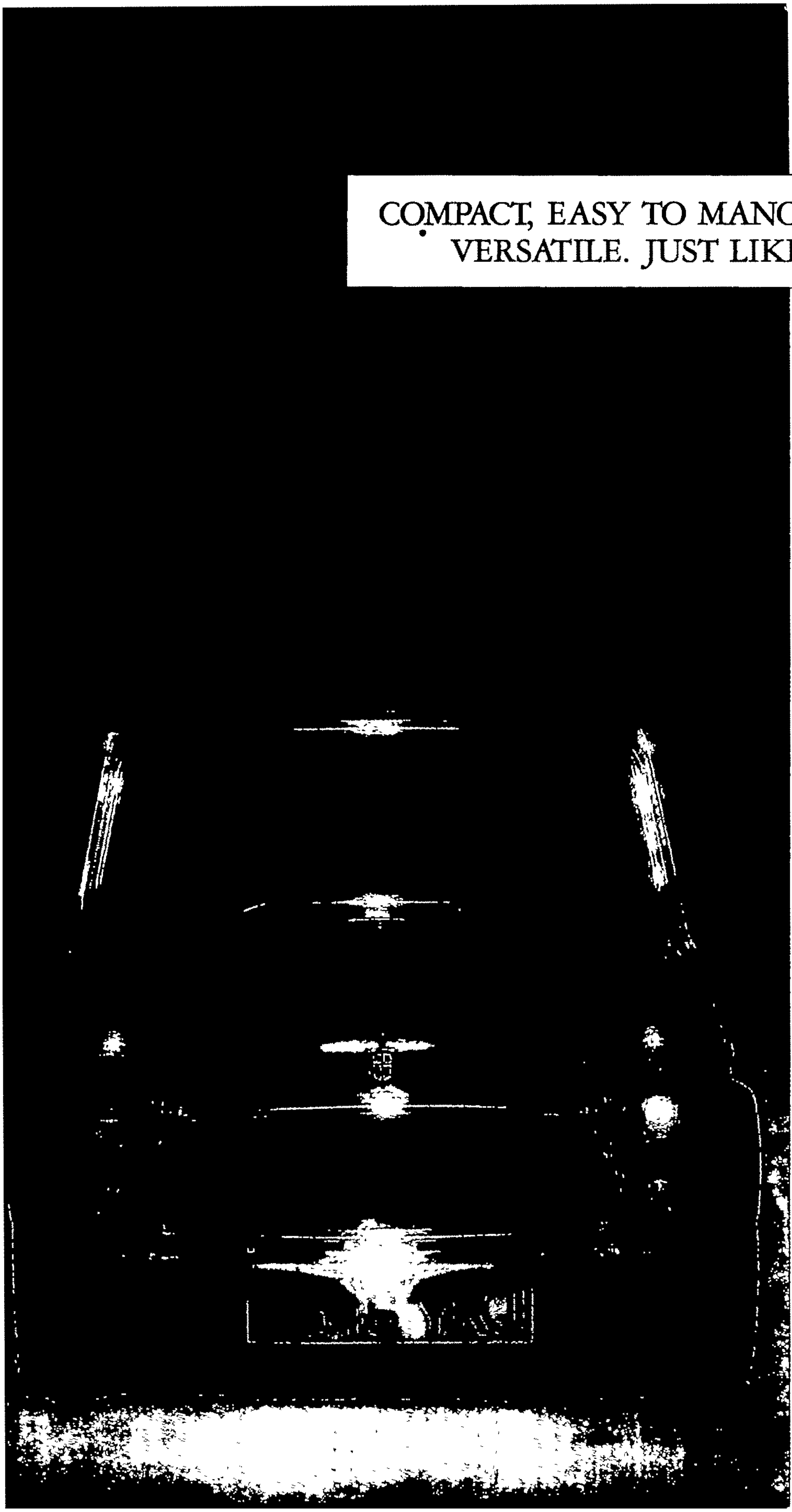

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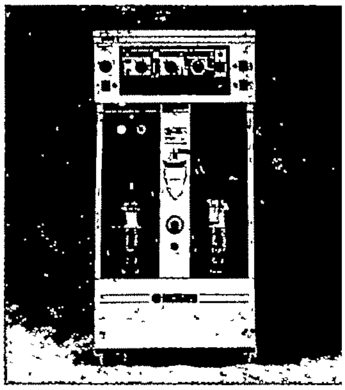

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REVIEW

A Urinary Detergent and Urolithiasis

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A feature of some of the tubular systems of the body is the establishment of mechanisms whereby blockage of the lumen is avoided by degrading or digesting the particulate matter coursing through the channels, so facilitating the elimination and expulsion of unwanted material. In the case of the vascular system, thrombi and fibrinous clots are digested by the proteolytic enzyme plasmin, which helps to ensure that the lumen of the vascular tree remains patent. In the urinary tract, blood clots are dispersed by urinary fibrinolytic activity and it seems reasonable to explore further the possibility that this mechanism may also be responsible for cleansing the pathways of other debris, and perhaps even be responsible for attempting to prevent the formation of potential obstructing agents such as stones.

Calcium Stones

The factors responsible for the formation of the many different types of stones have been intensively studied and although urologists have come to the point where virtually all calculi can be cleared from the urinary tract with either non-invasive or minimal interventional therapy, only a minority of stone formers (*i.e.* those with primary hyperparathyroidism or with cystine and pure uric acid stones) can be reassured that all the causative factors have been identified and be virtually guaranteed a cure. The majority continue to form further stones—15% 1 year after the first stone incident, 45% after 4 years and 66% after 9 years (Coe, 1980). Calcium stone disease accounts for about 70% of all urinary calculi seen in the Western world. It is clear that 6 factors are involved in this disorder: urine volume and pH, the concentration of the urinary crystalloids calcium, oxalate and uric acid, and the presence and nature of urinary mucopolysaccharides (Robertson *et al.*, 1978). These have been labelled as the 6 risk factors in calcium stone disease of the urinary tract, and correction of deviations from normal in these factors could be expected to prevent further stone formation. Urinary calcium is probably the factor most studied.

In a series of 108 patients seen at the Mayo Clinic with idiopathic calcium urolithiasis (*i.e.* those in whom primary hyperparathyroidism, sarcoid, Cushing's disease, *etc*, had been excluded) and followed up for a mean of 5 years, a high fluid intake and sensible limitation of the intake of dairy products halted new stone formation or stone growth in 58% (this included some hypercalciurics) (Hosking *et al.*, 1983). This has been called "the stone clinic effect". The authors recommended that all idiopathic stone formers should be managed on this simple conservative regime and be carefully followed up for evidence of continuing urolithiasis. Those who continued to exhibit active urolithiasis would require detailed investigation and appropriate therapy. This approach of a continuing follow-up programme makes a considerable impact on the workload of a department and implies a special interest in stone disease. The cost-effectiveness of this philosophy has to be compared with undertaking routine investigation of calcium measurements (3 blood samples and three 24-h urine collections) in all stone patients and discharging those with normal values from follow-up, recognising that a sizeable number will continue to form new stones or have continued stone growth. This latter approach may be acceptable in a busy department committed to providing a comprehensive urological service to a large local population. A further alternative is to prescribe thiazides as preventive therapy, recognising that these drugs are effective in lowering the urinary calcium excretion, which is

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probably the most important risk factor in calcium stone disease. However, in a double-blind control clinical trial of 62 patients with recurrent idiopathic renal calculi (irrespective of urinary calcium excretion levels), 2 groups were given either 7.5 mg of bendrofluazide daily or a placebo (Brocks *et al.*, 1981). Both groups demonstrated a similar reduction in stone formation. Kohri *et al.* (1987) showed that thiazides reduced urinary calcium excretion for 3 months, but that at 6 and 12 months the levels reverted to the pre-treatment values. Hence the observed reduction in stone formation is presumably due to "the stone clinic effect" and there are convincing reasons for adopting the Mayo clinic protocol referred to above.

In a carefully supervised group of 124 stone formers with idiopathic hypercalciuria studied at the Institute of Urology in London (Marickar and Rose, 1985), the urinary calcium was brought into the normal range, yet over one-half continued to develop new or larger calculi. It follows that there must be other unidentified factors which are partly responsible for the continued urolithiasis and a possible explanation for this lies in the sixth listed risk factor, the urinary mucopolysaccharides. These are also known as glycosaminoglycans and are said to inhibit the crystallisation of urinary calcium salts. It is more logical to think of these macromolecules in terms of size and that for a given volume of these substances, the smaller the aggregates the greater the surface area available for the adsorption of crystalloids. It is, I believe, through this mechanism that there exists a urinary detergent activity.

Urinary Macromolecules

Mucopolysaccharides and mucoproteins are high molecular weight compounds, best defined as proteins firmly bound to a carbohydrate (the latter containing hexosamine and/or hexose, sialic acid and fucose); they differ in respect of the protein content, this being predominant in the mucoproteins, whereas the carbohydrate is the major moiety in a mucopolysaccharide. The composite term macromolecule or colloid is alternatively used to describe these mucosubstances.

Urinary macromolecules are constituents of normal urine (about 470 mg daily) (King *et al.*, 1958) and the size of the compounds varies from 28 million daltons (the largest polymers of the Tamm-Horsfall mucoprotein) to less than 1000 daltons. It has been shown that the urinary macromolecules are substrates of plasmin (the active fibrinolytic enzyme) (Charlton, 1969) and this results in the larger macromolecules being disaggregated into smaller particles. That this actually occurs is confirmed by noting that the Tamm-Horsfall mucoprotein is seen in a number of different sizes, namely as polymers of 28, 14, 7, 3.5 and 1.7 million daltons and that these are immunologically identical, the polymers being made up of repeating units arranged end-to-end and side-to-side and linked by sialic acid molecules. This dispersion of the colloids by the naturally occurring phenomenon of urinary fibrinolytic activity (UFA) results in a relative increase in the surface area of the colloidal polymers. The colloids are negatively charged and adsorb onto their surfaces cations such as calcium. The greater the sub-division of the macromolecules the greater the surface area available for the absorption of, for example, calcium. This explains the phenomenon of the metastable zone present in normal urine, whereby the solubility products of calcium and oxalate are exceeded, yet nucleation and crystallisation do not occur, since the chelation of these inorganic ions avoids supersaturation and concrement formation. It has been shown that in stone formers, all of the urinary macromolecules are larger than 50,000 daltons (Drach *et al.*, 1982), whereas in the normal individual, two-thirds of the total macromolecules are smaller than 30,000 daltons.

It can be inferred from the above that the reason for the presence of the larger colloids is a decrease in UFA and that individuals with stone disease would also have a decrease in this parameter. That this is the case has been demonstrated by a study of 188 stone-formers, in two-thirds of whom the UFA was decreased as compared with controls (Charlton and Osmond, 1986). In other words, 2 specimens of urine containing equal amounts of calcium and urinary macromolecules were dissimilar in terms of whether the urinary colloids exhibited a detergent and beneficent function (due to most of the polymers being small and so preventing crystalluria) or were associated with concrement formation (in which the larger colloidal particles feature). Boyce and King (1959) stated that the mucosubstances were an essential ingredient in the genesis of stone formation and formed the skeletal framework on which the crystalloids adhered. The larger colloidal particles tend to aggregate (Van der Waals attractive forces) and this is countered by the proteolytic enzyme activity of urinary fibrinolysis, the function of which is to depolymerise the urinary macromolecules.

Circulating and Urinary Fibrinolysis

Fibrinolytic activity is determined by the balance of various pro-enzymes, namely plasminogen activators, plasminogen activator inhibitors and antiplasmins. Irrespective of whether they are related to circulating, urinary or tissue fibrinolytic activity, these pro-enzymes are produced by the vascular endothelium. It follows that the changes in circulating and urinary fibrinolytic activity can be expected to occur simultaneously. A decrease in the production of plasminogen activator by the vascular endothelium will result in decreased UFA, as is seen in stone disease; the decrease in circulating fibrinolytic activity is known to be associated with degenerative vascular and ischaemic heart disease. This therefore prompts a search for circumstantial evidence to support the concept that disordered fibrinolysis is common to both of these disease processes, recognising that there are many other factors which contribute to the development of these abnormalities. Three different avenues offer support for an association between cardiovascular disease and the formation of urinary calculi.

The first relates to the findings of Vermooten (1941) in South Africa, who dissected 1060 kidneys. Four years previously, Randall (1937) had described calcified plaques on the renal papilla, which in his view were the nidus of renal calculi. Vermooten found that Randall's plaques were present in 4.3% of the kidneys of the Bantu compared with 17.2% of those of Caucasian stock; he also observed the relative increase of these plaques in patients described as cardiacs and arteriosclerotics. These findings led him to speculate whether there was a connection between the disease processes responsible for arteriosclerosis and the deposition of Randall's plaques.

Of further interest is the possible relationship between the anatomical findings described above and the changes observed in the fibrinolytic activity of the Bantu and arterial disease. The Bantu living in South Africa are remarkably free from cardiovascular disease and the blood fibrinolytic activity of the male Bantu is greater than that of his Caucasian counterpart (Walker, 1961); when the former becomes Westernised, however, the prevalence of heart disease rises, with a relative decrease in circulating fibrinolytic activity compared with that of their forefathers (Meade *et al.*, 1978). Similarly, renal stone disease is virtually unknown in the Bantu living in South Africa (Vermooten, 1941). When members of the race migrate to the United States, their successors (the American negro) form renal stones as frequently as the rest of the American population (Dodson and Clark, 1946). Since it is not possible for a genetic mutation to become established in a large cohort within a few generations, these changes must be attributable to altered environment and/or diet.

Decreased Detergent and Stone Formation

A decrease in the production of plasminogen activator has been noted when the circulating triglycerides (Glas-Greenwalt *et al.*, 1984) and cholesterol levels are raised, demonstrating that the activity and function of the vascular endothelial cells are modified by the blood constituents flowing over them. A comparison of protein intake and fat consumption with hospital incidence of urolithiasis, as observed in 3 areas with differing levels of economic development (Anderson, 1973), revealed a well defined relationship detailing an increasing stone incidence with an increase in the dietary constituents mentioned; this is not dissimilar to that seen in cardiovascular degenerative disease. Recent work from Bloemfontein in South Africa (Beukes *et al.*, 1987) supports this concept in so far as the composition of renal stones in the current black population is becoming substantially different from that described in earlier surveys and it may be approaching that of their white compatriots. A change in the dietary pattern in blacks is occurring which is also reflected in the increasing incidence of ischaemic heart disease, which may also be responsible for the observed changes in renal stones.

Hence I would argue that the disturbance of a basic physiological mechanism (fibrinolysis) by a dietary change is a contributory cause of the increased prevalence of both degenerative vascular disease and renal stone disease and that this comes about by the decreased detergent activity in both the circulatory and urinary systems as a result of changes induced in the vascular endothelium. It therefore seems prudent to consider the organic component present both in urine and in stones as an important contributor to stone formation and its prevention. In this context I suggest that a significant untried approach in attempting to prevent further stone formation is to raise the lowered UFA to its normal effective detergent level by using an appropriate fibrinolytic enhancer such as an anabolic steroid (Walker and Davidson, 1978) or a biguanide (Hocking *et al.*, 1967). It will be 10 years before the benefit or otherwise of the suggested treatment will be apparent, by which time it will be possible to make an authoritative statement defining the significance of this urinary detergent in stone disease.

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AIDS: The Contamination Risk in Urological Surgery

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Summary—Increasing numbers of patients infected with the Human Immunodeficiency Virus (HIV) will be encountered in surgical practice. The risk of exposure to the virus during urological surgery is unknown. In an attempt to quantify the risk and to identify procedures that require change, 427 consecutive urological operations were prospectively assessed for contamination of the surgeon's skin, face and mucous membranes by potentially infected body fluids. Contamination occurred in 136 procedures (32%), of which 37 of 123 (30%) were open operations and 99 of 304 (33%) were endoscopic. Contamination of the face and eyes accounted for 46% (46 of 99 operations) of the contamination occurring in endoscopic surgery. Attention must be paid to reducing exposure of the surgeons' skin to patients' body fluids. The surgeons' eyes should be protected by modification of urological techniques and equipment to avoid spillage.

Infection with the Human Immunodeficiency Virus (HIV) has now become worldwide. Recent estimates given by the Chief Medical Officer to the Department of Health and Social Security (DHSS) suggest that between 5 and 10 million people have been infected throughout the world, of whom 10 to 30% will develop the full blown Acquired Immune Deficiency Syndrome (AIDS). If the present rate of progression continues without counter measures, up to 100 million people may be infected within the next 5 years (Tindall and Lansdowne, 1987). The problem is greatest in the United States, with a projected annual death rate from AIDS of between 142,000 and 201,000 by 1991. Since the condition is not a notifiable disease, accurate figures are unavailable, but the problem is of a smaller scale in the United Kingdom, where an estimated 30,000 people are currently infected (Tindall and Lansdowne, 1987). The voluntary monitoring system operated by the Communicable Disease Surveillance Centre (CDSC) and the Communicable Diseases (Scotland) Unit indicated a total of 1344 patients with AIDS in the UK in February 1988, of whom 749 had died (CDSC, 1988). An annual doubling in the rate of new cases seems to be the trend internationally, which would indicate that 1200 new cases can be expected in the UK in 1988 (Office of Health Economics, 1987).

From these gloomy figures it can be concluded that surgeons are certain to encounter HIV positive patients more frequently and must be prepared to cope with the problems that will result, particularly the infective risk constituted by such patients.

There have been authoritative articles based on studies of health care workers involved in the direct and indirect care of HIV positive patients who show a low incidence of seroconversion after needle stick injury. These indicate that the risk of infection from HIV positive patients is small (Geddes, 1986; Adler, 1987a). However, in view of the variable period before antibodies develop and the fact that the development of overt signs and symptoms of AIDS may take 5 years or more, we are not yet in a position to assess the risk accurately, although a more recent review stated that 1% of HIV infected needlestick injuries, or mucous membrane exposure, led to seroconversion (Adler, 1987b).

Surgeons are at particular risk since they encounter large quantities of blood and body fluids in association with sharp instruments used during complex manipulative manoeuvres. Penetrative or "needlestick" injuries are frequent, Hussain *et al.* (1988) reporting accidental injuries in 5.6% of their procedures. Glove punctures may be found in 3% of pairs before surgery (Guy *et al.*, 1988) and, during

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surgical procedures, glove puncture rates of between 37.5% (Brough *et al.*, 1988) and 50% (Lafferty and Wyatt, 1987) have been found. A penetrative injury has always been regarded as carrying the highest risk even if "a microtransfusion of infected blood" was required for seroconversion (Adler, 1987b). However, details from the Centre for Disease Control, Atlanta, (Nature, 1987) concerning 3 health care workers who had become seropositive in the absence of any needlestick injury and therefore, it is presumed, as a result of the passage of small quantities of infected blood through injured or inflamed skin or mucous membranes, has undermined this confidence. The recent death from AIDS of a surgeon in the UK has further served to focus the surgeon's mind on this problem and its management.

Precautions are obviously required and all routine surgical procedures require re-appraisal to reduce the risk of infection. General guidelines from the DHSS recommend the use of methods already familiar from the care of patients known to carry Hepatitis B antigens (DHSS, 1986). As most consideration has been given to the risks involved in open surgery, we are not aware of any study of the contamination risks in routine urological procedures, particularly during endoscopic surgery. We have, therefore, prospectively assessed the extent of contamination in our urological practice in an attempt to define potential sources of infection. Once identified, these occurrences must be reduced as far as is practicable.

Method

We prospectively recorded details of all operations performed at this hospital between September and December 1987. Open procedures included the most common urological operations with a bias towards oncological, andrological and reconstructive surgery. Gowns, gloves, masks and plastic aprons were worn during every open procedure. We made no attempt to change existing routine procedures and during this period we identified only 2 high risk patients requiring anti-hepatitis precautions. They were excluded from the analysis.

Gloves and plastic aprons were worn for all endoscopic procedures. Woven cotton gowns were added for more complex procedures, including all planned resections of prostate or bladder. Masks were seldom worn and protective visors or goggles were used for laser cases. Continuous irrigation resectoscopes were used in 6 of the 59 prostatic resections.

We recorded any contamination of the surgeon, or assistant, with either blood, blood-stained irrigation fluid or bloody urine. We particularly noted needlestick injuries, glove perforations without apparent penetration of the skin, facial (especially mucous membrane exposure) and, finally, exposure of the skin elsewhere when the duration of exposure was prolonged (arbitrarily defined as greater than 5 min).

Gloves were examined during the operation if glove injury was suspected and at the end of the procedure. Glove perforations were recorded if a glove was obviously torn or pierced or if it became evident from the presence of blood inside a glove that a previously unnoticed perforation had occurred.

Results

The range and practice of endoscopic surgery at St Peter's Hospital mirrors many more general units. In particular, there were no cases involving percutaneous renal surgery and only 3 ureteroscopies. An analysis of procedures performed is shown in Table 1.

A series of 405 patients underwent a total of 427 procedures (Table 2). The overall incidence of operations during which the surgeon became contaminated was 31.9% (136 of 427 operations) with a marginally higher rate of contamination in endoscopic operations (33%) compared with open procedures (30%) (Table 3).

Certain events leading to contamination of the surgeon's face during endoscopic surgery were identified and are detailed in Table 4. Table 5

Table 1 Endoscopic Operations at St Peter's from September to December 1987

Operation	*No.*
Cystoscopy	120
Cystoscopy + other procedure (ureteric catheter, diathermy, phenol inj., bladder wash-out)	27
Cystoscopy + trans-rectal U/S + biopsy	24
Cystoscopy + urethral dilatation	3
Optical urethrotomy	11
TURP	59
Bladder neck incision	14
TUR bladder tumour	31
Laser (to penis, urethra, bladder, etc.)	11
Looposcopy + ureteroscopy	2
Ureteroscopy	1
Pelviscopy	1

Table 2

Total no. of patients		405
Total no. of procedures		427
	open procedures	123
	endoscopic	304
Surgeon	RSO	306
	Consultant	121

Table 3 Overall incidence of operations during which surgeon was contaminated (136/427 = 31.9%)

Incidence of contamination	
open surgery	37/123 = 30.1%
endoscopic	99/304 = 32.6%

Table 4 Contamination During Endoscopic Surgery

Identifiable events leading to contamination of face during endoscopic surgery	
Splash from catheter channel/instrument port	22
"Clicking"/cleaning loop	13
Tubing problems	9
Splashes from Ellick evacuators	8
Anaesthetic straining/cough	8
Assorted drips and splashes	4
Draining bladder	2
Obturator jerk	1
Glove to face	1
68 contamination events during 46 endoscopic operations	
Contamination of trunk and limbs	
Drainage of effluent/irrigant on to trunk and limbs	52
Cystourethroscopy with patient supine	1

Table 5 Contamination During Open Surgery

Identifiable events leading to contamination during open surgery		(Face, Limb, Trunk)
Glove perforations	27	L
Needlestick/penetrating injury	10	L
Arterial spurters	5	F
Seepage of fluids through gown	4	LT
Scalpel stab	3	L
Diathermy injury	1	L
Retractor injury	1	L
51 events in 37 operations		

indicates events leading to contamination during open surgery.

Discussion

Hospitals within the Bloomsbury area have extensive experience of AIDS patients. Advice circulated locally (though not to the surgical staff of this hospital!) now warns that all human body fluids be regarded as "high risk" and describes the precautions to be taken. These precautions are generally applied in the major centres of the AIDS epidemic in the United States. Furthermore, the DHSS (1986) suggests that "the procedures described amount to little more than what are usually regarded as part of good clinical practice". The implications are that precautions are generally required, at least in high risk areas such as London, and that failure to take them could, in the event of infection occurring, be regarded as resulting from poor standards of practice. It is not known if this would have consequences for pensions (or other benefits) usually payable as a result of illness resulting from an occupational exposure. Negotiations are currently taking place between the profession's representatives and the DHSS concerning arrangements for doctors becoming seropositive for HIV.

A contamination risk during endoscopic urological surgery was to be expected, but the extent of the risk (32.6%) surprised us. We have included all "significant" contamination, although it could be argued that much of the recorded soiling of intact skin should be discounted. Intact skin may be an effective barrier but we are unclear as to the protection afforded by "wet" skin when exposed to body fluids for prolonged periods. In addition, the skin may not be entirely free from abrasions or areas of inflammation that may weaken its qualities as an anti-viral barrier. In the present circumstances, surgeons should be very cautious about continuing the previous casual exposure of their skin to potentially infected fluids and the general use of waterproof gowns, rather than permeable, should be encouraged.

Whatever the arguments over the importance of contamination of the skin of the trunk or limbs, there is general agreement concerning the infective risk from contamination of the face, mucous membranes, and particularly the eyes, which we found accounted for nearly half (46%) of all the contamination in endoscopic surgery. Such exposure must be avoided or prevented.

What we have recorded is part of the general experience of every urologist, but it has never before been quantified or identified so rigorously. Certain events commonly lead to contamination, especially draining the bladder, which is highly likely to cause some degree of splashing of the surgeon's face, particularly if the patient coughs or strains and if the bladder is overfilled. Efforts can be made to remove the surgeon's face from the "firing line" by the use of videocamera attachments or, in future, endoscopes with light sensitive chips rather than optical elements. This would allow examination and resection at a distance, guided by an image on a conveniently placed screen. We found the use of Ellik evacuators without a locking fitting to the resectoscope sheath to be particularly prone to splashing. Fundamentally, a system of irrigation with drainage of both blood-stained fluid and tissue fragments into a closed drainage system should be developed to avoid these manoeuvres which put both surgeon and theatre staff at risk.

It may be suggested that existing equipment and methods may continue to be used in safety. Certainly, if the patient is known to be in a high risk group, then "anti-hepatitis" type precautions can be taken. However, even though a careful sexual, drug and medical history should be taken, particularly in young men, it is unrealistic to expect all high risk cases to be identified. If current predictions are correct, we will be faced with a large number of HIV positive patients, most of them asymptomatic and increasingly outside the present high risk groups. Traditional endoscopic surgery with visors or goggles is more difficult, slower, less accurate and may still allow contamination. Changes are required now that will enable us to perform comfortably, accurately and safely for all concerned, including the patient, whether known to be HIV positive or not.

The further development of rapid tests for the presence of HIV viral antigens should replace the relatively crude, and initially inaccurate, antibody assays presently available and may make possible the accurate assessment of the patient's status prior to operation.

We found the incidence of contamination during open urological procedures very similar to the incidence reported for general surgical operations (Brough *et al.*, 1988). Glove perforations were found on 42 occasions in 123 operations, though our study relied on a simple visual assessment and it is therefore likely that the true incidence of perforation was higher. Most injuries occur during wound closure, particularly if a mass closure technique is used (Hussain *et al.*, 1988). Surgeons are often not aware that their gloves are damages even when there is evidence of skin puncture (Guy *et al.*, 1988).

Although we did not initially look at skin injury prior to surgery, we began to note instances when the surgeon operated with injured (or at least non-intact) skin as the implications of the study became clearer. It was our impression that some degree of skin injury, particularly to the fingers, was common especially after such popular social pursuits as gardening, sailing or even as a result of "scrubbing up". There is an obvious need for the development of a much stronger, yet sensitive glove, analogous to the developments in condoms! A viricidal cream applied before donning surgical gloves might provide another acceptable barrier to infection.

Extra care must clearly be taken with any surgery involving high risk groups and such precautions will have to be applied more widely. Apart from the increase in the cost of equipment and materials, one fundamental effect will be reduced throughput in surgical units as a direct result of the extra time required for safe surgery. This must be included in the measurement of performance indicators and in manpower planning.

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Idiopathic Hydronephrosis: Diagnosis, Management and Outcome

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Summary—The results of the diagnosis, management and treatment of 50 consecutive patients presenting with renal pelvic dilatation suggestive of pelviureteric junction obstruction are presented. Modern assessment methods were used to investigate both pre-operative status and also the results of management of the 37 obstructed and 13 non-obstructive patients. The role and influence of the new assessment techniques on clinical decision making are discussed.

Significant improvements in the methods available for the assessment of renal function and upper urinary tract urodynamics have been introduced in the past decade. These have improved the diagnosis of pelviureteric junction obstruction and the distinction between obstructive and non-obstructive hydronephrosis. The management of this condition and its consequences have thus changed during this time. We report the results of a prospective study of 50 patients during a period when the newer techniques were available.

Patients and Methods

The study group comprised 50 patients seen over a period of 5 years in whom the diagnosis of pelviureteric junction obstruction was suspected on intravenous urography. Following urography, all patients proceeded to further assessment using the techniques listed in Table 1. The protocol required that any patient in whom the diagnosis of pelviureteric junction obstruction was suspected on urography proceeded directly to standard diuresis renography. This was performed using ^{123}I-hippuran and a dedicated Scintronix gamma camera computer system, giving frusemide 0.5 mg/kg (40 mg in adults) at the 20-min point after the radiopharmaceutical. The split renal function in each diuresis renogram was measured by calculating the standard 2–3 min blood background-subtracted uptake in individual kidneys and expressing them as a percentage of the injected dose (O'Reilly *et al.*, 1986). This technique gave an objective, quantitative value for percentage split renal function and an unmodified view of upper tract urodynamics before and after the administration of frusemide. Unequivocally obstructed patients were listed for surgery. Unequivocally unobstructed patients were followed up as out-patients with further general urological assessment and diuresis renography at 6-monthly intervals. Equivocal cases proceeded to modified diuresis renography, giving the intravenous frusemide 15 min before the radiopharmaceutical to maximise the urinary flow rate (English *et al.*, 1982; Upsdell *et al.*, 1988). If this did not classify the hydronephrosis, perfusion pressure flow studies or parenchymal transit time studies were available. When required, perfusion pressure flow studies were performed taking note

Table 1 Techniques Available for the Assessment of Idiopathic Hydronephrosis

Diuresis urography
Standard diuresis renography (F+15)*
Modified diuresis renography (F−15)†
Parenchymal transit time studies
Perfusion pressure flow studies

* Frusemide given 20 min after radiopharmaceutical.
† Frusemide given 15 min before radiopharmaceutical.

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of the recommended protocols of Whitaker (1982) and Pfister (1982). Renal pelvic puncture was carried out in the radiology department under local anaesthesia, inserting a percutaneous transparenchymal pig-tail catheter into the renal pelvis using X-ray control, or ultrasound if function was impaired. The pressure flow study was performed the following day using Lectromed UIS 5000 urodynamic equipment and a syringe pump capable of perfusing at 10 to 20 ml/min. Parenchymal transit time studies were available according to the technique described by Whitfield *et al.* (1978).

Patients with significant obstruction who underwent surgery had post-operative diuresis renography at 6 weeks, 3 months, 6 months and thereafter as necessary, particular interest focusing on changes in underlying renal function and improvements in drainage from renal pelvis to ureter. Equivocal post-operative patients, in whom it was not possible to be sure of the objective success of surgery, proceeded to modifed diuresis renography and thence to perfusion pressure flow studies as appropriate.

Results

The series comprised 28 males and 22 females aged between 5 and 64 years (mean 43). There were 8 children (<16 years). The presenting symptoms are listed in Table 2 and complicating features in Table 3. The results of pre-operative investigations are demonstrated in Figure 1; 43 patients were classified on the basis of standard diuresis renography (36 obstructed; 7 non-obstructed); 7 were equivocal. These were clarified by modified diuresis renography (1 obstructed, 6 non-obstructed). Perfusion pressure flow studies and parenchymal transit time studies were not required at this stage (see below).

Of the 37 obstructed patients, 30 underwent pyeloplasty, 4 had endopyelotomy and 2, both elderly females, refused treatment and have remained in a state of "compensated hydronephrosis" (Koff, 1987). An elderly patient had a primary nephrectomy. Pyeloplasty was performed according to the Anderson-Hynes dismembered technique. Twelve patients had sump drainage only with neither splint nor nephrostomy. One of these required secondary double-J stent insertion for a 2-week period for persistent fistula, with no lasting sequelae; 18 patients had both sump drain and splint/nephrostomy using a Cummings tube; 1 patient had a secondary nephrectomy. Post-operative drainage, as measured by diuresis renography, improved in 26 of the 30 cases (86%) and function, which was reduced in 22 cases, improved in 16.

Table 2 Presenting Complaints in 50 Consecutive Cases of Idiopathic Hydronephrosis

	No.
Pain only	38
Pain with UTI	4
Pain on drinking	2
Haematuria only	2
Haematuria on exercise	1
Haematuria (traumatic)	1
Renal colic	1
Chance finding	1

Table 3 Complicated Hydronephrosis

Complicating features	*Treatment*	*No. of patients*
Hydronephrosis in solitary kidneys		
Obstructed	Pyeloplasty	3
Non-obstructed with associated calculi	Pyelolithotomy only	2
Non-obstructed		2
Bilateral hydronephrosis		
Bilateral obstruction	Bilateral pyeloplasty	1
Unilateral obstruction, contralateral non-obstructive dilatation	Unilateral pyeloplasty	2
Bilateral non-obstructive dilatation with calculi	Pyelolithotomy	1
Bilaterial non-obstructive hydronephroses		1
Renal calculi		
In obstructed cases	Removed at Pyeloplasty	3
In non-obstructed cases	Pyelolithotomy	3
	Percutaneous nephrolithotomy	1

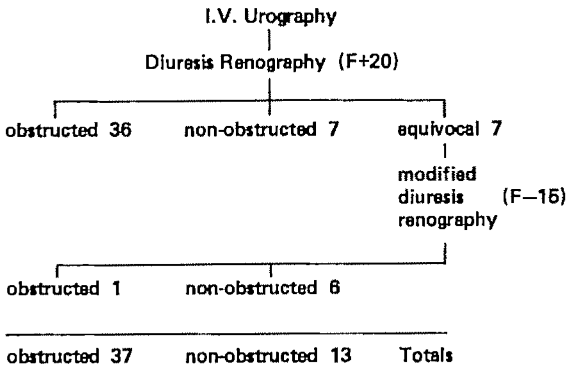

Fig. 1 Results of investigation of 50 consecutive cases of renal pelvic dilatation.

Analysis by Student's t test and Wilcoxon paired sums test showed improvement in both mean and median function to be highly significant ($P < 0.001$). The degree of improvement was greatest in those patients with the most severely depressed pre-operative function (Fig. 2).

In 4 post-operative patients the objective results were equivocal and further evaluation was required (Fig. 3). They could not be clarified by standard and modified diuresis renography. One was lost to follow-up but 3 had perfusion pressure flow studies and none was found to be obstructed. All had reduced function and renal pelvic capacities >300 ml—conditions known to make diuresis renography unreliable. Although the patients were asymptomatic, perfusion pressure flow studies were invaluable to reassure both patient and clinician that the obstruction had indeed been relieved and no further surgery was required.

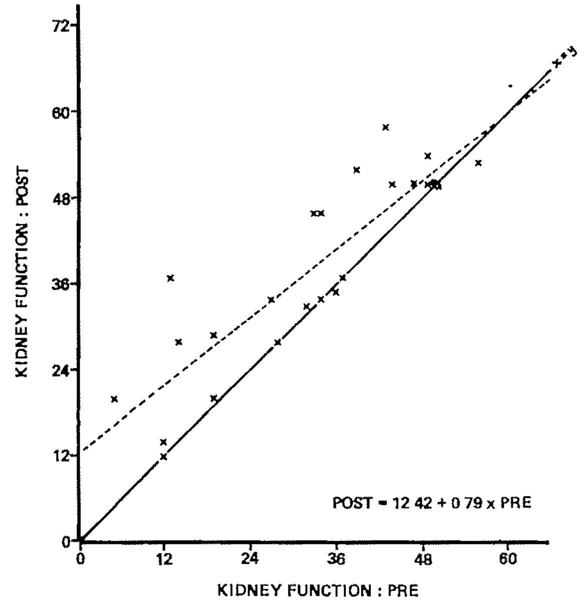

Fig. 2 Functional results of surgery for hydronephrosis Graph of pre- and post-operative split function scores in 26 patients undergoing Anderson Hynes pyeloplasty (data on split function not available in 4 cases—1 nephrectomy, 3 pyeloplasty in solitary kidneys)

No patient with non-obstructive dilatation has shown deterioration in function or drainage during the course of the study.

Discussion

During the past decade, new techniques have been introduced to help the urologist to assess accurately and quantitatively renal function and drainage through dilated upper urinary tracts, to evaluate genuinely obstructed cases and to identify cases of non-obstructive dilatation with all the implications of that diagnosis. Thus a fundamental change in the management and outcome of idiopathic hydronephrosis (pelviureteric junction obstruction) has occurred.

Idiopathic hydronephrosis is not a homogeneous condition. The cause of the failure of transmission of pelvic to ureteric peristalsis is not known, although the underlying dyskinesia producing the obstructive condition can present in several forms and be accompanied by several associated features (Fig. 4). The complicated hydronephrosis rate in the present series involved the occurrence of the condition in single kidneys (14%), the occurrence of bilateral cases (10%) and the coexistence of renal calculi (14%). Pre-operative urinary infection oc-

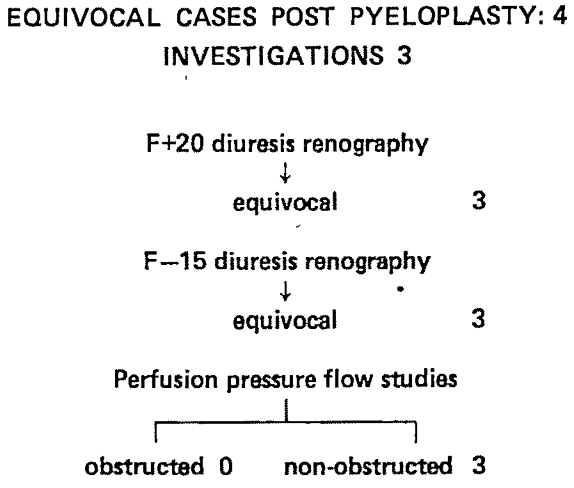

Fig. 3 Investigation of equivocal post-operative cases.

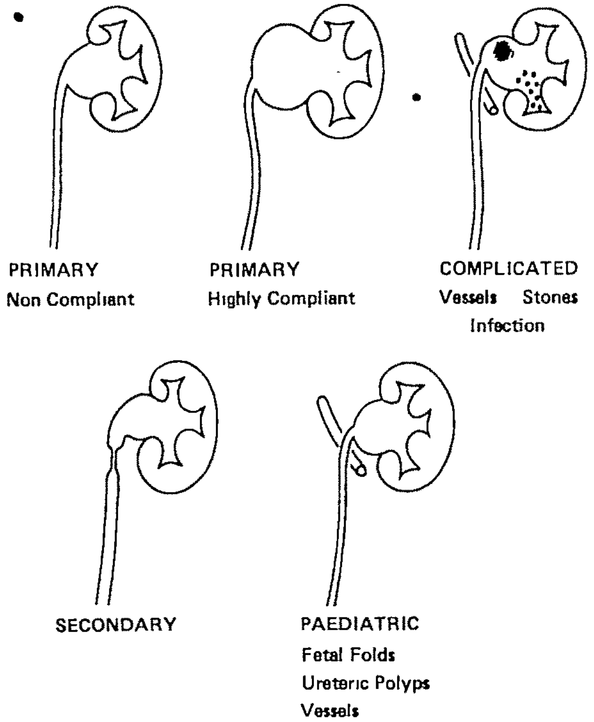

Fig. 4 Different types of idiopathic hydronephrosis.

curred in only 4 patients (8%). These complications were divided almost equally between the renographically obstructive and non-obstructive cases. This has important management implications. For example, patients with stones in non-obstructive systems should require simple stone removal, usually by ESWL or percutaneous nephrolithotomy, without pyeloplasty, while obstructive patients will require consideration of both, by whatever method is appropriate—a distinction impossible before the advent of dynamic evaluation. Similarly, before objective testing, when all decisions were made on urography alone, it would have been difficult to leave a significantly dilated renal pelvis in a solitary kidney without surgery, and to follow it up conservatively by urography alone. With objective testing, such a decision can be taken with confidence, as it was in 4 (8%) of the patients in this series. Such an approach results in a significant and desirable reduction in unnecessary surgery and the tailoring of appropriate surgery to particular requirements.

The evaluation of medical problems should proceed in a logical direction, reserving invasive procedures for patients in whom simpler evaluation has failed. None of the patients reported here had pre-operative perfusion pressure flow studies; it was judged that diuresis renography performed carefully, examined critically and interpreted in conjunction with other relevant data always gave a reliable urodynamic assessment. The routine use of ^{123}I-hippuran, the responses to which are rapid and more easily interpretable than ^{99m}Tc-DTPA (O'Reilly *et al.*, 1977), examination in the erect position after bladder emptying, with a second void towards the end of the test if necessary, and the introduction of modified (F-15) diuresis renography have reduced the equivocal response rate of the test and diminished the need for other procedures in this condition. Nonetheless, the success of the radionuclide procedure was somewhat surprising and might not be maintained in a larger series. In patients with massive pelvic dilatation, or severely depressed renal function, perfusion pressure flow studies may be required to guide the clinician towards a management decision, as in the 4 post-operative equivocal cases described above. Post-operative standard and modified diuresis renography had both failed to give a clear result; split function was reduced pre-operatively in all cases and was unchanged post-operatively in 3, slightly improved in 1. Diuretic-induced washout remained poor in all 4 patients; the 3 with depressed post-operative function were available for further study. All had perfusion pressure flow studies and were found to be non-obstructed. All had renal pelvic volumes >300 ml. Diuresis renogram interpretation depends on a prompt diuretic response to washout retained tracer from the upper tract in a short period of time. A large renal pelvic volume will be slow to fill and emptying may be delayed considerably until the pelvis is full. Reduced renal function will result in a reduced diuretic response and contribute to slow renal pelvic filling (Upsdell *et al.*, 1988). These conditions influence the value of diuresis renography, which must be interpreted with care under such circumstances.

In this study, 86% of pyeloplasty cases showed post-operative improvement in drainage through the pelviureteric junction as assessed by renography. The post-operative split renal function results are of equal interest. Several previous studies have attempted to define functional improvement after surgery for PUJ obstruction with conflicting results (Bratt *et al.*, 1977; Parker *et al.*, 1981; Kinn, 1983; Samuelson *et al.*, 1984; King *et al.*, 1984; Djurhuus *et al.*, 1985). The present study was entirely prospective and included all age groups. The operations were performed according to an established technique by one surgeon. Split renal function was studied quantitatively pre- and post-operatively in the same nuclear medicine laboratory at fixed intervals, according to established protocol, and all tests were performed using ^{123}I-hippuran. The statistically significant improvement in function not only demonstrated the success of dismembered pyeloplasty for this condition but also underlined the inherent ability of the kidney to recover from intermittent or chronic obstructive uropathy. This was emphasised by the finding that the greatest improvement was seen in patients with the most severely compromised pre-operative renal function. This was also the conclusion of a recent study into the potential for renal functional improvement following relief of bilateral chronic obstructive uropathy secondary to high pressure chronic retention of urine (Jones *et al.*, 1987). The potential for renal recovery, particularly relevant to the growing kidney, should never be underestimated, and the primary nephrectomy rate in pelviureteric junction obstruction should be low.

One of 12 pyeloplasty patients who had sump drainage alone required a secondary nephrectomy for urinoma formation secondary to silent anastomotic disruption leading to a non-functioning kidney. While single cases are anecdotal, such an event strengthens the case for post-operative internal splintage with or without nephrostomy. No problems other than 2 urinary tract infections were encountered in the 18 patients where Cummings tubes provided both of these functions. Nephrostograms were performed on the sixth post-operative day to exclude extravasation and, following clamping for 24 h, the tube was removed. This method was preferred to double-J stents for internal splintage as long as the latter required an anaesthetic for subsequent retrieval. With the advent of flexible cystoscopic removal and magnetic splints to avoid this, double-J stends could offer an alternative method of post-operative splintage, with earlier discharge from hospital in some cases.

Four patients with uncomplicated primary obstructive hydronephrosis had endopyelotomy during the latter part of the study; 2 improved and did not need further procedures; 2 were no better and have had pyeloplasties. It is too soon to agree with some that the advent of endopyelotomy means that "pyeloplasty is now redundant" (Wickham, 1987). Either a randomised prospective comparison between pyeloplasty and endopyelotomy or a report of long-term results from centres with more experience of endopyelotomy, preferably using quantitative functional and urodynamic assessment methods for a reasonable (>2 years) follow-up period, are required before reaching firm conclusions on this point.

Thirteen patients had renographically dilated non-obstructed systems. None of these, including the 4 patients with solitary kidneys and the 6 renal units in those with bilateral hydronephrosis, has shown deterioration in function or drainage during the course of this study, supporting previous reports on this subject (O'Reilly *et al.*, 1981; English *et al.*, 1982; Kass *et al.*, 1985). Of over 250 children and adults included in these reports, only 1 has shown deterioration requiring pyeloplasty and this was identified easily during follow-up by routine diuresis renography. However, vigilance is required to avoid missing such cases, missing silent deterioration (Malek, 1983) or misdiagnosing intermittent hydronephrosis as non-obstructive megacalicosis (O'Reilly, 1989). No patient with renal pelvic dilatation should be discharged until a suitable period of follow-up with objective testing has taken place and the clinician is satisfied that he is dealing with a stable condition.

In conclusion, idiopathic hydronephrosis may be obstructive or non-obstructive. The obstructive form remains a common cause of obstructive uropathy. The results of pyeloplasty in such cases are good as measured by improvement in split renal function and pelvic to ureteric drainage. The long-term results of endopyelotomy remain unknown. Modern assessment methods have changed the clinical approach to the condition. They have helped to demonstrate the difference between obstructive and non-obstructive hydronephrosis, have provided reliable means to monitor conservative management and have allowed objective assessment of the results of surgery. Correlation between the various techniques has not always been good (Poulson *et al.*, 1987) for various reasons (Upsdell *et al.*, 1988). This underlines the need to explore the principles behind the techniques, the need to investigate discrepancies in individual cases by attention to technique, underlying renal function, urinary flow rates, *etc*, and the need to improve the performance, interpretation and standardisation of the procedures. Recent advances have made a measurable impact on the assessment of pelviureteric junction. There will always be some equivocal results but they represent a shrinking minority.

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Dietary Habits in Renal Stone Patients Compared with Healthy Subjects

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Summary—The dietary habits of renal calcium stone patients were investigated both by dietary history and by 4-day food records and compared with the dietary habits of control subjects, matched on the basis of age, sex, social and professional status. The method using 4-day records seemed to be more precise, judged by the correlation to the urinary output of nutrients. There was no difference in the daily intake of major nutrients between stone formers and controls, but a higher ingestion of vitamin C in controls and a larger consumption of alcohol among stone formers. In contrast to some epidemiological evidence, there were no significant differences in consumption of animal protein when stone formers were matched for social class. Despite a similar total intake of calcium, the stone formers excreted more calcium in the urine, probably reflecting a higher intestinal absorption of calcium. There seem to be only marginally different dietary habits between stone formers and carefully matched control subjects. Differences in the urinary output of minerals and electrolytes are mainly due to variations in gastrointestinal uptake.

It has been suggested that dietary factors have played an important part in the increase in renal calcium stone disease in the Western world during the last few decades (Andersen, 1973). It has been shown that dietary protein is the nutrient most closely related to the frequency of stone disease at several different demographic levels (Robertson *et al.*, 1981a). A high dietary protein has also been shown to cause an increase in the excretion of urinary constituents important for calcium stone formation, such as urinary calcium and oxalate (Robertson *et al.*, 1979; Fellström *et al.*, 1984), urate (Coe *et al.*, 1976; Robertson *et al.*, 1979; Fellström *et al.*, 1983) and a decrease in the excretion of citrate (Fellström *et al.*, 1984). The validity of this finding may be judged by comparing the dietary habits of calcium stone formers and control subjects. In a controlled study of dietary habits, based on interviews of stone formers and controls, no difference could be found regarding the major nutrients, and only a higher intake of fibre in healthy controls (Griffith *et al.*, 1981). These conflicting reports prompted us to carry out the present study. Since dietary habits may vary with social structure and degree of affluence, we considered it important to select control subjects matched not only for age and sex but also for social status and also to compare 2 methods of estimating dietary habits.

Patients and Methods

A group of 20 patients with recurrent calcium stone disease attending our out-patient stone clinic was studied. There were 15 males and 5 females with an average age of 44 ± 13 years. They had not previously been given any specific dietary advice but only general recommendations concerning the advantages of a high fluid intake, which, however, according to our experience, was difficult to implement. Six patients who were on prophylactic thiazide treatment for stone formation stopped their medication 2 weeks in advance of the study. A control group was obtained by asking the stone

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patients to select a person of the same age and sex and with a similar socio-economic status and working habits, but without renal stone disease and not taking any medication. They usually chose a workmate.

The stone patients and controls were asked to keep a 4-day food record by household measurement of their dietary intake (Marr, 1971). They were also interviewed by a dietician regarding their dietary habits using a version of an early dietary history method (Burke, 1947). Through a computerised procedure the nutrient content of the dietary records and the dietary histories were calculated. The nutrient data on the foodstuffs were based on food tables (Swedish National Food Administration, 1978). During the period of dietary records and interviews, the patients and the controls also collected urine samples during two 24-h periods. These were analysed with respect to components believed to be important for stone disease, including calcium, magnesium, sodium, phosphate, urate, oxalate and citrate. The reliability of the 2 methods of assessing dietary intake was judged by the correlation between the estimated dietary intake and the measured urinary excretion of the corresponding nutrient. The dietary intake of protein, sodium, potassium, phosphate and calcium according to the 4-day records and the dietary histories was thus correlated to the urinary excretion of total nitrogen, sodium, potassium, phosphate and calcium. Urinary nitrogen has been regarded as a validity test in dietary surveys (Isaksson, 1980).

Conventional statistical methods were used for calculation of means, standard deviations and linear correlations and Student's t test for comparison of mean values. A multivariable discriminant analysis based on 5 of the dietary nutrients with the highest individual discriminative potential was also performed. A model based on the measurement of the generalised squared distance between the groups was used.

Results

The dietary data from the 4-day records correlated well with the urinary excretion, whereas the data obtained by the dietary histories did not (Table 1). Furthermore, data obtained by dietary histories were on an average ≅15% higher than the 4-day records. Dietary data from the 4-day records were therefore mostly used in this study.

There was no difference in the dietary intake of the major nutrients in stone formers compared with controls, except for a higher intake of vitamin C in the male controls than in the male stone formers (Table 2). Males consumed more fat and had a higher caloric intake than females, together with a higher body weight.

Table 1 Comparison between 4-day Recordings and Dietary History (daily intake) and Correlation with Urinary excretion of Corresponding Nutrients in Stone Formers and Controls

Nutrient	*4-day recordings*	*Dietary history*
Protein (g) (urinary nitrogen)	84±20 r=0.52 $P<0.001$	102±24 r=0.22 $P<0.22$
Sodium (g)	2.36±0.64 r=0.39 $P<0.02$	2.96±0.90 r=0.01 $P<0.91$
Potassium (g)	3.20±0.70 r=0.38 $P<0.02$	4.20±1.0 r=0.22 $P<0.2$
Phosphate (g)	1.43±0.35 r=0.30 $P<0.08$	1.80±0.50 r=0.19 $P<0.28$
Calcium (g)	0.96±0.36 r=0.14 $P<0.4$	1.29±0.52 r=0.09 $P<0.6$

According to the 4-day records, there was no difference in the average consumption of alcohol between the 2 groups (Table 2) but there were 8 stone formers who consumed hard liquor compared with 4 controls ($x^2=4$, $P<0.05$). From the dietary history it was also revealed that the stone patients consumed more alcohol (13.2±11.0 g/day) than the controls (6.9±6.3 g/day, $P<0.05$) (Fig. 1).

Stone formers excreted more calcium than the controls (Table 3), although they tended to have a lower intake of calcium (Table 2). The quotient of dietary intake/urinary excretion of calcium was 19±10% in controls and 36±22% in stone formers ($P<0.005$) (Fig. 2). Moreover, male stone formers excreted more phosphate and sodium than male controls, whereas no difference was observed in urinary urate, citrate or oxalate.

The discriminant analysis based on the dietary intake of vitamin C, calcium, purine, phosphate and fibre (Fig. 3) gave a correct classification of 26/37 subjects ($P<0.05$). Based on the urinary excretion of calcium, sodium, phosphate, urate and oxalate, the discriminant function gave a correct classification of 25/35 subjects ($P<0.02$).

Discussion

Dietary factors have been suggested as important determinants of renal stone formation, responsible

Table 2 Daily Dietary Intake of Nutrients, Minerals and Vitamins (4-day records) in Stone Formers and Controls (mean ± SD)

	Stone formers		*Controls*	
	Males	*Females*	*Males*	*Females*
Body weight (kg)	82±12[a]	73±15	82±10	64±4
Nutrients				
Protein (g)	87±24	78±26	87±15	75±14
Fat (g)	112±26[b]	89±23	111±25	93±22
Carbohydrate (g)	267±80	254±49	298±75	257±50
Fibre (g)	12.9±4.4	17.3±3.2	15.5±4.8	14.7±2.9
Purine (mg)	168±51	174±62	153±60	132±59
Alcohol (g)	10.6±11.6	5.7±3.4	7.6±10.4	4.1±5.1
Minerals				
Sodium (g)	2.4±0.7	2.1±0.3	2.5±0.7	2.1±0.20
Potassium (g)	3.3±0.8[b]	2.8±0.6	3.4±0.5	2.7±0.61
Calcium (g)	0.91±0.43	0.76±0.20	1.07±0.30	1.0±0.34
Phosphate (g)	1.40±0.44	1.30±0.30	1.54±0.20	1.3±0.37
Iron (mg)	20±6	19±6	20±5	17.3±0.60
Vitamins				
Vitamin C (mg)	69±33[c]	112±52	119±61	125±41
Thiamine (mg)	1.7±0.6	1.5±0.8	1.7±0.4	1.3±0.3
Riboflavin (mg)	1.7±0.5	1.7±0.8	1.8±0.4	1.5±0.3
Niacin-equival (mg)	28±7	26±12	25±6	22±4

[a] $P < 0.01$, males compared with females.
[b] $P < 0.05$, males compared with females
[c] $P < 0.01$, stone formers compared with controls

for several of the characteristic urinary risk factors of stone disease (Robertson *et al.*, 1981a; Fellström *et al.*, 1983, 1984). Several studies have focused on dietary protein, which correlated well with affluence and prevalence of stone disease (Robertson *et al.*, 1981a). In a population of vegetarians, on the other hand, the prevalence of stone disease was lower than expected (Robertson *et al.*, 1981b).

A diet enriched with protein causes changes in urinary composition which discourage stone formation. There is an increase in urinary calcium (Fellström *et al.*, 1984), probably due to reduced tubular reabsorption (Allen *et al.*, 1979) and an increase in oxalate (Robertson *et al.*, 1979) because of an increased load of precursor amino acids (Gambardella and Richardson, 1977; Hodgkinson, 1977). Urinary urate also increases (Coe *et al.*, 1976; Robertson *et al.*, 1979; Fellström *et al.*, 1983) as a result of the increased purine load and *de novo* synthesis of urate (Zöllner, 1976), together with a decrease in urinary pH (Fellström *et al.*, 1983) and urinary citrate (Fellström *et al.*, 1984).

If the hypothesis that dietary protein is important for renal calcium stone disease is valid, one would expect stone patients to have a higher consumption of protein than healthy subjects, provided that intestinal absorption is similar. In making such a comparison it seems important to match the control subjects not only for age and sex but also for social status and working situation, which may be decisive factors in dietary habits. Using an elaborate matching system for such factors, no difference in the dietary intake of the major nutrients could be detected in this study, which is in accordance with previous diet record studies in renal stone disease (Power *et al.*, 1984). Stone formers seemed to have a higher dietary intake of vitamin C, which contradicts previous reports (Power *et al.*, 1984). A high intake of vitamin C among the controls may reflect a consumption of fruit and vegetables, corresponding to the higher dietary intake of fibre by controls reported previously (Griffith *et al.*, 1981) but not confirmed in later studies (Power *et al.*, 1984) or by the present study. The level of vitamin C intake, 80 to 120 mg daily, was not of a magnitude that would influence urinary oxalate significantly, even though ascorbic acid is a major precursor of oxalate formation (Gambardella and Richardson,

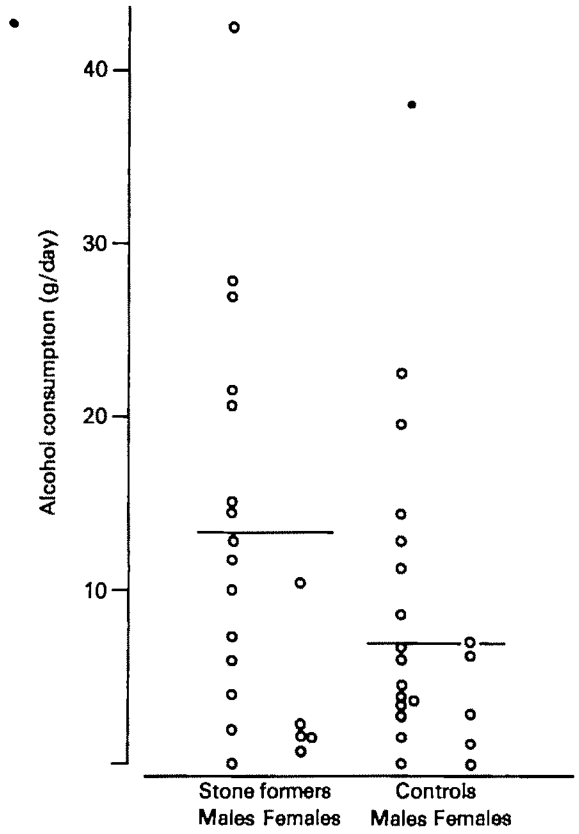

Fig. 1 Alcohol consumption according to dietary history (g/day) in stone formers and controls ($P<0.05$).

1977). It seems that a consumption of several grams of ascorbic acid is needed to produce a change in urinary oxalate.

There was no difference in the amount of calcium ingested by stone patients compared with controls, but their urinary excretion was higher; this is in accordance with previous studies (Pak *et al.*, 1974; Robertson *et al.*, 1978; Ljunghall *et al.*, 1980; Wilkström *et al.*, 1983). The quotient of urinary excretion/dietary intake of calcium can be regarded as an estimate of calcium absorption, provided that the subjects are in calcium balance. Thus it may be concluded that calcium absorption was higher ($P<0.005$) among the stone patients, which is in accordance with previous measurements on calcium absorption (Pak *et al.*, 1974; Ljunghall *et al.*, 1977).

The dietary intake of phosphate was similar in stone formers and controls and was also equal to the average daily intake in Swedish individuals. Despite a similar intake of phosphate, stone formers had a higher urinary excretion of phosphate. The reason for this is not obvious but the phosphaturia could be associated with the increased sodium excretion ($P<0.01$), since there is evidence that sodium and phosphate have some common steps in tubular reabsorption (Lau *et al.*, 1980). The relationship between sodium metabolism and the renal handling of calcium and phosphate in stone patients needs to be studied further.

The 2 methods for assessing dietary habits seemed to differ in precision. The correlation between the urinary excretion of a nutrient and the assessed dietary intake may be used to estimate the precision of the methods. We found positive correlations between the 4-day recordings and the corresponding urinary output during the same 4 days in all nutrients except calcium. However, similar correlations between dietary intake and urinary excretion of calcium were found within the classes of stone formers and controls (not shown),

Table 3 24-hour Urinary Excretion (mmol/24 h) in Stone Formers and Controls (mean ± SD)

	Stone formers		*Controls*	
	Males	*Females*	*Males*	*Females*
Calcium	6.6 ± 1.3[a]	6.1 ± 2.0	4.8 ± 2.0	4.5 ± 2.1
Phosphate	39 ± 14[b, c]	31 ± 6	29 ± 8	21 ± 3
Sodium	200 ± 51[c]	171 ± 40	157 ± 41	131 ± 35
Potassium	76 ± 18	71 ± 9	70 ± 16	60 ± 12
Urate	4.3 ± 1.1[b]	3.8 ± 0.5	3.8 ± 0.7	3.1 ± 0.9
Citrate	3.5 ± 1.4	3.7 ± 1.0	3.1 ± 0.7	3.6 ± 0.8
Oxalate	0.41 ± 0.10	0.38 ± 0.10	0.36 ± 0.11	0.32 ± 0.06
Urea	374 ± 81[b]	318 ± 61	347 ± 90	270 ± 103
Nitrogen	846 ± 176[b]	716 ± 137	785 ± 192	614 ± 215

[a] $P<0.005$, stone formers compared with controls
[b] $P<0.05$, males compared with females.
c $P<0.01$, stone formers compared with controls

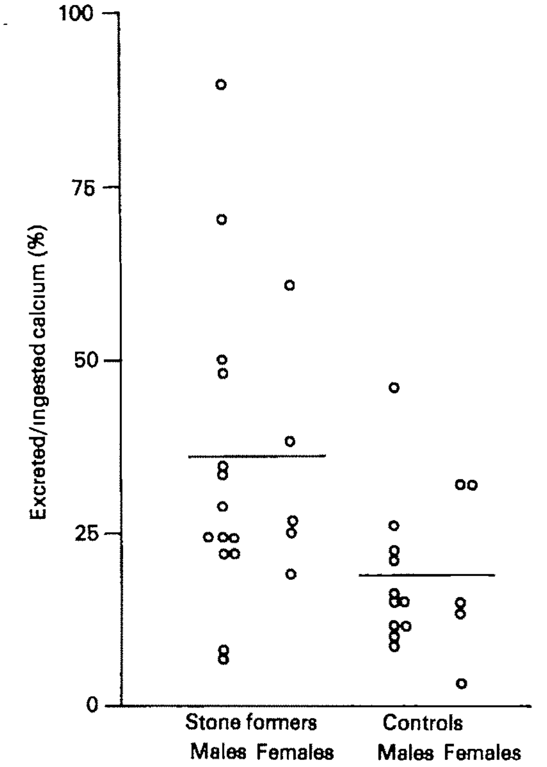

Fig. 2 Excreted/ingested calcium (%) in stone formers and controls ($P<0.005$)

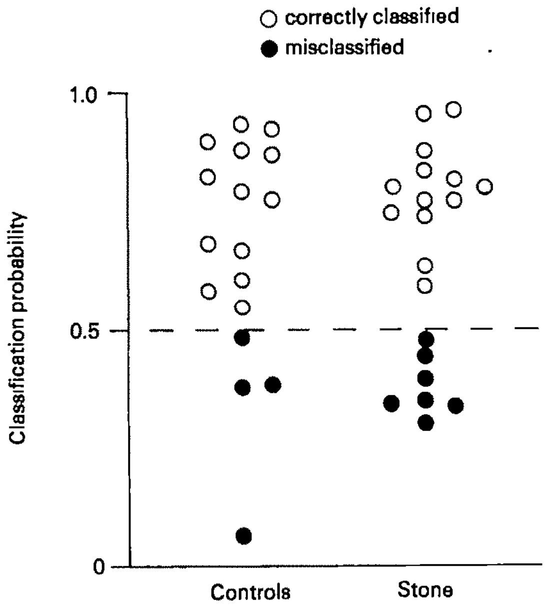

Fig. 3 Discriminant analysis based on dietary intake of vitamin C, calcium, purine, phosphate and fibre ($x^2 \cong 4.8$, $P<0.05$).

because of distinct differences in calcium absorption between the groups.

The importance of alcohol consumption in stone disease is uncertain. Four-day records during weekdays may not be an appropriate method, even though there were more stone patients than controls drinking hard liquor during these 4 days. From the dietary history data it could be shown that stone formers had a higher consumption of alcohol than the controls (Fig. 1).

Since there was no single nutrient, apart from vitamin C, which was significantly different between the patients and the controls, a multifactorial model for discrimination of patients and controls based on diet was constructed, including the 5 nutrients with the highest t-value between the groups. A discriminant function could be calculated which classified two-thirds of the patients correctly ($P<0.05$). However, as 11/37 individuals were misclassified, the usefulness of the discriminant function is doubtful. When the discrimination was based on the urinary constituents with the highest t values, the discrimination was slightly better ($P<0.02$), but 10/35 patients were still misclassified. A better discriminant function could probably have been achieved, based on the urinary values of a larger number of patients and controls, and be used to estimate the probability of a patient belonging to either group.

It was concluded that there are probably no major differences in the dietary habits of calcium stone patients compared with carefully selected controls, matched on the basis of age, sex, social and professional status.

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Screening Renal Stone Formers for Distal Renal Tubular Acidosis

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Summary—A group of 110 consecutive renal stone formers were screened for distal renal tubular acidosis (RTA) using morning fasting urinary pH (mfUpH) levels followed by a short ammonium chloride loading test in patients with levels above 6.0. In 14 patients (12.7%) a renal acidification defect was noted; 13 had incomplete and 1 had complete distal RTA. Distal RTA was found particularly in recurrent stone formers (17%), and especially in those with bilateral stone disease, where a distal renal tubular acidification defect was found in 50%.

We have been unable to differentiate primary from secondary RTA in renal stone formers. Regardless of whether the acidification defect is primary or secondary to stone formation, however, all renal stone formers with distal RTA can expect to benefit from prophylactic alkaline therapy and it is recommended that the screening procedure, which is easy to use in daily clinical practice, is applied to all stone formers and not restricted to patients with recurrent stone disease.

The success of improved techniques in stone removal might lead some to underestimate the importance of screening procedures to unmask metabolic disturbances in the management of urolithiasis. From the point of view of prophylaxis this would be inadvisable.

Williams and Chisholm (1976) documented the value of stone screening and follow-up. They found that 60% of stone formers had a treatable metabolic abnormality. One of the most common abnormalities was incomplete distal RTA.

To evaluate the importance of distal renal tubular acidification defects in daily clinical practice we screened all patients admitted with urolithiasis over a 1-year period.

Patients and Methods

The series comprised 110 consecutive, non-uraemic patients (41 females, 69 males) (median serum creatinine 94 mmol/l, range 60–169). The median age was 55 years (range 16–87). Twenty patients had bilateral and 90 had unilateral stone disease; 70 patients were recurrent stone formers and 40 were admitted with their first stone episode. Three patients had medullary sponge kidney, 2 had primary hyperthyroidism and 3 had pure urate stones. The diagnosis of urolithiasis was confirmed urographically in each case.

The initial screen consisted of measuring the morning fasting (8 h) urine pH (mfUpH) using a pH meter (Radiometer, Copenhagen). Subjects whose mfUpH was above 6.0 were further evaluated with a short ammonium chloride loading test. Each patient, after fasting for 6 h, was given 0.1 g/kg ammonium chloride orally as a solution over a 45-min period. To ensure adequate diuresis 100 ml of water were given every hour during the test. The urine pH was measured hourly for 4 h after the ingestion of ammonium chloride using a pH meter. To document adequate systemic acidification, plasma bicarbonate was measured at 2 and 4 h. Pre-ingestion samples were also collected. The interpretation of the test is summarised in Table 1.

There were no dietary restrictions. Patients with positive urine cultures were not examined until at least 1 negative culture was obtained. Patients with an established acidification defect commenced prophylactic treatment with sodium bicarbonate tablets 3 Meq/kg/day.

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Table 1 Screening Test

UpH > 5.4 and $p\text{-}HCO_3^- < 16$ mmol/l, distal RTA confirmed*
UpH < 5.4; distal RTA excluded
UpH > 5.4 and $p\text{-}HCO_3^- > 16$ mmol/l, test inconclusive

* If metabolic acidosis is present even in the normal condition the acidification defect is complete; otherwise it is incomplete (Modified from Pohlmann *et al*, 1984)

Results

In 22 patients (20%) the mfUpH was above 6.0 and they underwent an ammonium chloride loading test; in 14 cases (12.7%) the urinary pH did not fall below 5.4; 13 patients (11.8%) had incomplete distal RTA and 1 (0.9%) had complete distal RTA (Table 1). All patients developed adequate systemic acidosis on acid loading (median $p\text{-}HCO_3^- =$ 12 mmol/l, range 10–15). In patients with normal renal acidification the urinary pH usually falls well below 5.0 with a corresponding serum bicarbonate level below 16 mmol/l. In the group of 70 recurrent stone formers, distal RTA was found in 12 (17%). Two patients (5%) with a first stone episode had incomplete distal RTA. One of these had several stones in both kidneys; the other had only 1 minor stone but it caused massive stasis of the upper urinary tract. Four of 90 patients (4.5%) with unilateral stone disease showed impaired renal acidification, whereas the frequency in patients with bilateral stone disease was 50% (10/20) (Table 2). The acidification defects were equally distributed among males (7) and females (7), this means that the acidification defects were relatively more frequent in the females, 17% (7/41) compared with 10% (7/69) in the males.

Stone disease started early in life in stone formers with distal RTA, whose median age at the first stone symptom was 42 years (range 35–67) compared with 54 years (range 16–77) in patients without a distal acidification defect. In more than 60% of stone formers with distal RTA the onset of stone disease was before the age of 45 years compared with 40% in the remainder (Table 2).

Thirteen of the 14 patients with distal RTA had undergone 1 or more operations for stones (93%), whereas only 37 patients (39%) in the group without distal RTA had had operative treatment (Table 3).

None of the patients with urate stones had impaired renal acidification. Two of the 3 patients with medullary sponge kidney and 1 of the 2 patients with primary hyperparathyroidism had incomplete distal RTA.

Table 2 Details of Patients

	No acidification defect (n=96)		*Distal RTA (n=14)*	
Age at first stone symptom (years)	*n*	*%*	*n*	*%*
–19	5	5.2	1	7.1
20–24	3	3.1	2	14.3
25–29	8	8.3	2	14 3
30–34	8	8.3	0	0
35–39	7	7.3	2	14.3
40–44	8	8.3	2	14 3
45–49	13	13.5	0	0
50–54	17	17 7	0	0
55–59	10	10.4	2	14.3
60+	17	17.7	3	21 4

Table 3 Operative Treatment

	No acidification defect (n=96)		*Distal RTA (n=14)*	
Number of operations per patient	*n*	*%*	*n*	*%*
0	43	45	1	7
1	28	29	2	14
2	14	15	4	28
3	9	9	4	28
4	2	2	1	7
5			1	7
6			1	7

Discussion

In recent years a substantial incidence of abnormal renal acidification in recurrent stone formers has been reported (Williams and Chisholm, 1976; Citron-Nadal *et al.*, 1977; Backmann *et al.*, 1980; Anton *et al.*, 1984). If the acidification defect, as claimed by most authors, is the primary event in the pathological sequence of stone formation in renal stone formers with RTA, it should be possible to diagnose the defect through early screening before the stone disease becomes recurrent.

Previous studies on renal acidification in renal stone disease have been largely restricted to recurrent stone formers (Marquardt, 1973; Citron-Nadal *et al.*, 1977; Backmann *et al.*, 1980; Anton *et al.*, 1984). Our aim in this study was to describe the incidence and clinical importance of distal renal tubular acidification defects in renal stone disease as a whole, using a screening procedure that is simple and easy to use in daily clinical practice. Our results confirm that distal RTA in particular is associated with a severe form of stone disease, but that acidification defects can also be found in patients with short-term stone disease, although to a lesser degree. In the evaluation of which stone formers should be screened and at what stage in stone disease this should be done, the question of the pathological sequence in stone formers with RTA becomes especially important. At present 2 theories predominate:

1. Impaired urinary acidification precedes stone formation. This results in systemic acidosis (constant or intermittent), which causes increased urinary excretion of calcium and decreased excretion of citrate, and thereby promotes stone formation in an alkaline urine.
2. Impaired urinary acidification is a result of chronic stone disease. Chronic stone formation causes damage to tubular function, including the urinary acidifying ability. The induced acidification defect then maintains and reinforces stone formation through the development of hypercalciuria and hypocitraturia.

It is known that treatment with bicarbonate in these patients reduces stone frequency at the same time as the excretion of calcium and citrate returns to normal (Sebastian *et al.*, 1976). This observation has been used to support theory 1 (Backmann *et al.*, 1980; Anton *et al.*, 1984; Osther *et al.*, 1988). However, this does not dismiss theory 2 completely, since the reduction in stone frequency caused by alkaline therapy could also be explained by an elimination of the above mentioned reinforcement. It appears from our study that the incidence of distal RTA increases with the increasing severity of stone disease. This can also be explained using both theories, and our study does not specifically point to one or the other aetiology. However, whether patients have primary or secondary RTA, they can expect to benefit from prophylactic alkaline therapy, and until the aetiology of RTA in renal stone formers is firmly established, we recommend that screening be applied to all renal stone formers and not just to those with recurrent stone disease.

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The Effect of Glycosaminoglycans on the Crystallisation of Calcium Oxalate

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Summary—The effect of glycosaminoglycans on urinary stone formation was evaluated using a mixed suspension, mixed product removal (MSMPR) crystallisation system together with scanning electron microscopy (SEM) to examine the resulting crystals. Chondroitin sulphate was found to decrease the nucleation rate and to promote both the growth rate and suspension density. Results obtained with hyaluronic acid, although inconclusive, are similar to those given by chondroitin sulphate. Heparin sodium salt had a powerful inhibitory effect on both the nucleation rate and the suspension density, the effect increasing in proportion to the heparin concentration. SEM examination showed that the octahedral habit of calcium oxalate dihydrate was modified by the addition of heparin sodium salt and confirmed that the average crystal size in the presence of chondroitin sulphate and hyaluronic acid was significantly greater than the control or that found in the presence of heparin sodium salt.

In recent years a number of reports have discussed the mechanism of calcium stone formation and emphasised the important effects of both inhibitory and promotory materials. Despite widespread interest in this topic, however, the nature of such crystal inhibitors and promotors has not been fully elucidated.

It is generally believed that there are two major types of crystal formation inhibitors. The first are low molecular weight materials, such as pyrophosphate, citrate and magnesium, and they account for a relatively small percentage of total inhibitory activity. The second is macromolecular material consisting of glycosaminoglycans (GAGs), uromucoid and polyribonucleotide, *etc.* These appear to be major inhibitors and their role in the pathogenesis of calcium stone formation has received much attention. In particular, there are many reports about the effect of GAGs on calcium oxalate crystal formation. However, the reported findings have often been confusing and this may well reflect the wide variety of test systems used.

Robertson *et al.* (1973) showed that heparin and chondroitin sulphate had an inhibitory effect on the growth and aggregation of calcium oxalate crystals. The inhibitory effect of chondroitin-4-sulphate and chondroitin-6-sulphate was confirmed by Bowyer *et al.* (1979). Ryall *et al.* (1981) reported that heparin and, to a greater degree, chondroitin sulphate were responsible for the major portion of the inhibitory effect on aggregation of calcium oxalate crystals. The inhibitory effect of urine on crystal growth was attributed to the combined action of a number of inhibitors. Furthermore, the rates of crystal growth and aggregation in the presence of heparin and chondroitin sulphate were significantly increased after pre-treatment with sodium urate, indicating a reduction in the inhibitory potency of heparin and chondroitin sulphate by this salt (Ryall *et al.* 1986). Pak *et al.* (1979) showed similar results. Robertson and Scurr (1986) examined the effect of polyanionic inhibitors such as chondroitin-4-sulphate, heparin and ribonucleic acid (RNA) using a mixed suspension, mixed product removal (MSMPR) continuous crystalliser. RNA and, to a lesser extent, heparin and chondroitin sulphate were found to have

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inhibitory effects on the growth and aggregation of calcium oxalate crystal formation at normal urinary concentration. In contrast, all of these materials increased the nucleation rates when present at and above normal urinary concentrations.

It is well known that the structural components of GAGs are present in the matrix of urinary stones. Baba *et al.* (1983) extracted and identified matrix GAGs in calcium-containing urinary stone by 2-dimensional electrophoresis and showed that the main components of matrix GAGs were heparan sulphate and hyaluronic acid. Nishio *et al.* (1985) showed that the principal GAGs of stone matrix were heparan sulphate in calcium oxalate monhydrate, hyaluronic acid and heparan sulphate in calcium oxalate dihydrate, and hyaluronic acid in apatite. They also considered hyaluronic acid and heparan sulphate to be promoters of stone formation. Roberts and Resnick (1986) reported that the GAGs heparan sulphate, hyaluronic acid and, possibly, keratan sulphate had been identified in stone matrix. They presumed that GAGs were incorporated into the structure of the stone and may be intimately related to stone development and growth. All of these composition studies have shown that the most prominent urinary GAG, chondroitin sulphate, was absent from urinary stone matrix.

GAGs are polyanionic polysaccharide chains of variable length and seven or eight types of GAG are presently recognised. The different types of GAGs exist with varying frequency in different tissues. Approximately 250 mg of GAGs are formed daily, of which 10% are excreted in the urine (Kennedy, 1976). The origin of urinary GAGs lies in the human body tissue (Endo *et al.*, 1979). Urinary GAGs in normal subjects consist of approximately 60% chondroitin sulphate, 15 to 20% heparan sulphate, 15% keratan sulphate and 4 to 10% hyaluronic acid together with small quantities of other materials (Baba *et al.*, 1983; Roberts and Resnick, 1985). Robertson *et al.* (1973) reported that the urinary excretion of GAGs in stone formers was larger than that in control subjects, but some reports indicate no significant difference between the 2 groups (Baba *et al.*, 1983; Ryall and Marshall, 1983; Hesse *et al.*, 1986).

We report an attempt to evaluate the effects of heparin, chondroitin sulphate and hyaluronic acid on both the nucleation and the growth rates of calcium oxalate using the continuous MSMPR crystalliser method and subsequent examination of the resulting crystals using scanning electron microscopy.

Materials and Methods

Observations were made in the continuous MSMPR crystalliser system operating at 37°C as described previously (Rodgers and Garside, 1981; Li *et al.*, 1985; Kohri *et al.*, 1988). Table 1 specifies the composition of the two feed solutions making up the artificial urine used in the experiments. The calcium and oxalate concentrations were 12.0 and 1.0 mmol/l respectively, which are marginally higher than those found physiologically. At these higher concentrations, sufficient numbers of calcium oxalate crystals were produced to evaluate the effect of the GAGs. The pH of the mixture was 5.5. Other experimental details were as reported by Kohri *et al.* (1988). In particular, the average residence time, T = 6.5 min throughout, and the crystal size distribution between 6.1 μm and 19.1 μm, were used to calculate the growth and nucleation rates.

Three kinds of GAGs, chondroitin sulphate, hyaluronic acid and heparin sodium salt, were added to Solution II. Subsequently the solutions were filtered through a 0.3 μm Millipore filter. The final concentrations of chondroitin sulphate (Type A, sodium salt from whale cartilage) were 10^{-8}, 10^{-7} and 10^{-6} mol/l (assuming a relative molecular mass of 50,000), those of hyaluronic acid (Grade 1, from human umbilical cord) were 10^{-8}, 10^{-7} and 2.5×10^{-7} mol/l (assuming a relative molecular mass of 20,000), and those of heparin sodium (Grade I, sodium salt from porcine intestinal mucosa) were 10^{-8}, 10^{-7} and 10^{-6} mol/l (assuming a relative molecular mass of 25,000). These concentrations were similar to those occurring in human urine and to those used in previous studies (Ryall *et al.*, 1981, 1986). The GAGs were supplied by Sigma Chemical Co., St Louis, USA. The growth rate, G (μm/min), the apparent nucleation rate, B (no/min. ml), and the suspension density, M_T (mmol/l) were calculated according to the previously described relationship (Kohri *et al.*, 1988). Supersaturation ratio, S, and solubility product, K_s, were also obtained by the previous method (Kohri *et al.*,

Table 1 Recipe for Feed Solutions

Feed Solution I	*(g/l)*	*Feed Solution II*	*(g/l)*
Na_2SO_4	6.00	NaH_2PO_4 $2H_2O$	6.80
$MgSO_4$ $7H_2O$	3.45	Na_2HPO_4	0.87
NH_4Cl	4.65	$Na_3C_6H_5O_7.2H_2O$	1.17
KCl	12.14	NaCl	13.51
$CaCl_2$ $2H_2O$	3.53	$Na_2C_2O_4$	0.268
Sodium lauryl sulphate	0.04		

1988) on the assumption that the GAGs did not affect either the complexation of ions in the solution or the solubility of calcium oxalate.

At the end of the experiments, the crystal/solution mixture was filtered through a 0.2 µm Millipore and the crystals obtained were observed using scanning electron microscopy.

Results

Initial control experiments were performed in order to assess reproducibility in determining growth and nucleation rates by the continuous MSMPR crystalliser method. Five experiments were performed under identical conditions, and in the absence of GAGs, using the solutions specified in Table 1. Nucleation rates (B) and growth rates (G) were determined from the size distributions over a period of approximately 10 to 70 min (1.5 to 11 residence times) measured from the point when the two solutions were first fed to the crystalliser.

The results are shown in Figure 1. All 5 experiments showed highly reproducible results. The variation of B and G during the first 40 to 50 min of the run corresponded to the initial unsteady state period. After approximately 50 or 55 min (7.7 to 8.5 residence times), conditions became steady with time. This is in good agreement with theoretical studies which indicate that between 8 to 10 residence times are usually required to achieve steady state (Randolph and Larson, 1971). The mean and standard deviation of the nucleation and growth rates obtained from all of the data points after 55 min were $(8.88 \pm 0.86) \times 10^3$ no/min.ml and 0.421 ± 0.017 µm/min respectively. These results provided the control against which the effects of GAGs were assessed.

The supersaturation ratios were calculated as described previously (Kohri *et al.*, 1988) using computer programs developed by Werness *et al.* (1986). These make use of thermodynamic stability constants to calculate free ion activities for urinary ions, these same activities then being used to calculate the supersaturation ratios. The average steady state supersaturation ratio corresponding to the above values of nucleation and growth rates was 39.9.

Similar experiments performed in the presence of the various GAGs enabled nucleation and growth rates to be determined. Full details and results of these experiments are given in Table 2. The variation in supersaturation ratio between different experiments is comparatively small and arises from the varying amounts of crystalline calcium oxalate formed in different experiments. This in turn reflects the influence of the GAGs on nucleation and growth kinetics. At high concentrations, heparin sodium appears to have the greatest effect on the nucleation rate, reducing it to about 10% of the control value when present at a concentration of 10^{-6} mol/l. Conversely, chondroitin sulphate produces the largest increase in growth rate; at a concentration of 10^{-6} mol/l the growth rate is about 80% higher than the control.

The total mass of crystal in suspension is expressed as the suspension density, M_T (mmol/l) (Kohri *et al.*, 1988). Table 2 demonstrates the influence of the macromolecules on this quantity.

Table 2 Experimental Results

Macromolecule concentration (mol/l)	*Solution concentrations*					
	[Ca] (mmol/l)	*[Ox] (mmol/l)*	*S*	*B* $\times 10^{-3}$ *(no/min ml)*	*G (µm/min)*	M_T *(mmol/l)*
Control	11 94	0 94	39.9	8 9	0.42	0.065
(a) *Chondroitin sulphate*						
10^{-8}	11.88	0.88	37 3	5.7	0.61	0.13
10^{-7}	11 89	0.89	37 9	5 0	0.63	0.12
10^{-6}	11 84	0 84	36 1	3 9	0 74	0.16
(b) *Hyaluronic acid*						
10^{-8}	11.91	0.91	38.5	10.6	0.45	0.094
10^{-7}	11 92	0.92	39 3	3.3	0.63	0.079
$2 5 \times 10^{-7}$	11.97	0.97	41.4	2 6	0.50	0.031
(c) *Heparin sodium salt*						
10^{-8}	11 93	0.93	39 7	7 4	0 46	0.070
10^{-7}	11 98	0.98	41.9	1.8	0.47	0.019
10^{-6}	11 99	0.99	42.3	0 78	0.51	0.010

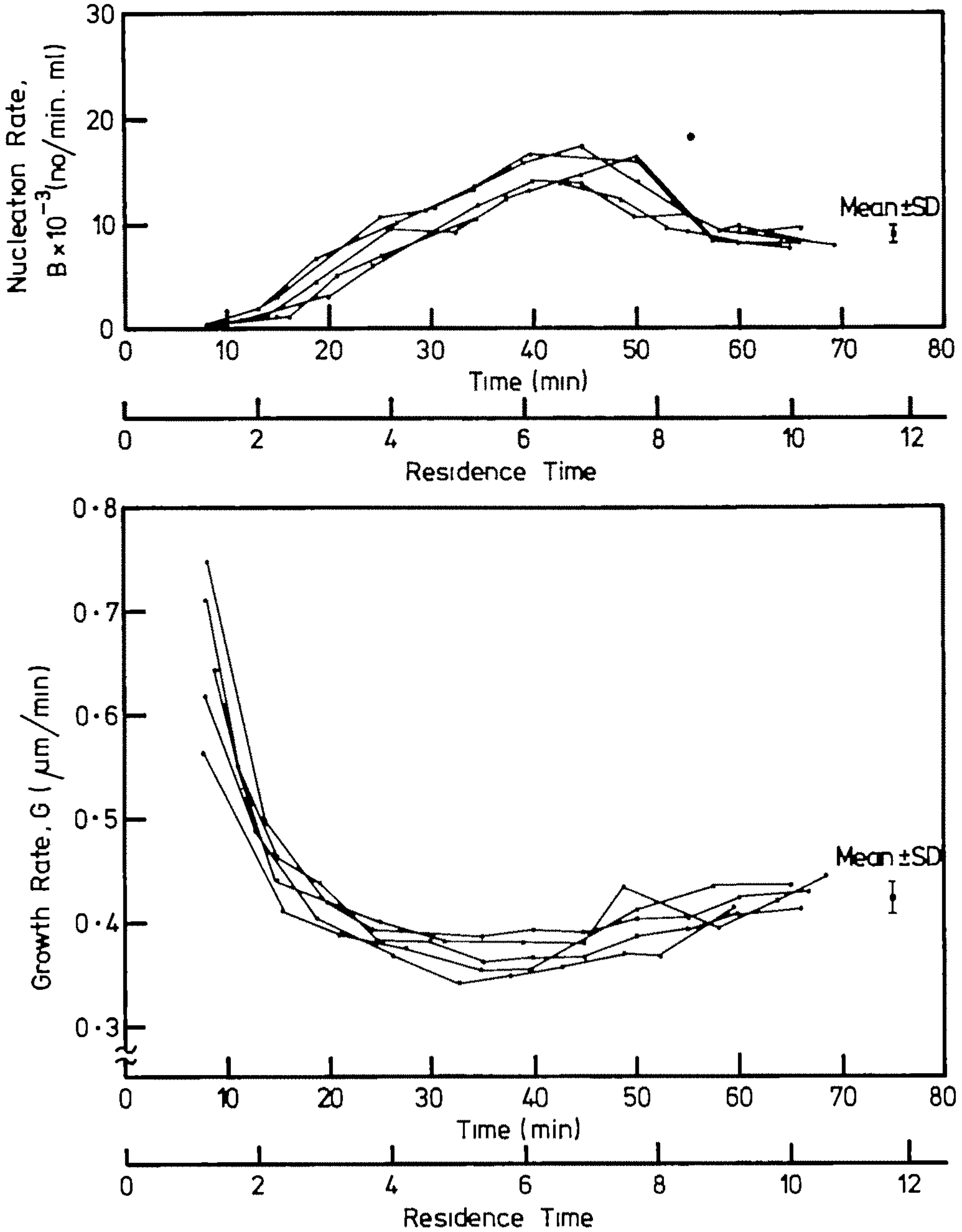
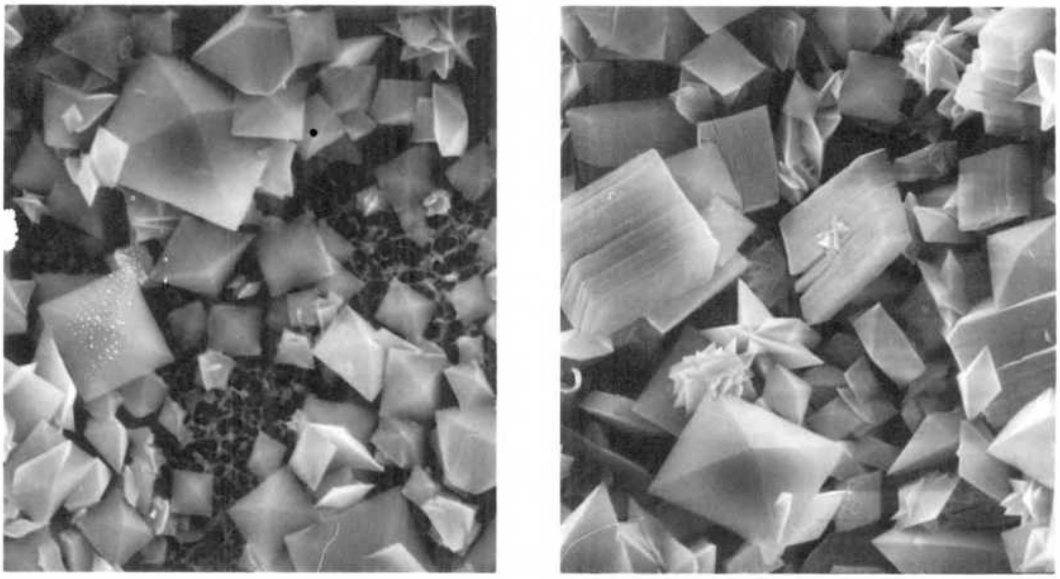


Fig. 1 Attainment of steady state nucleation and growth rates (control)

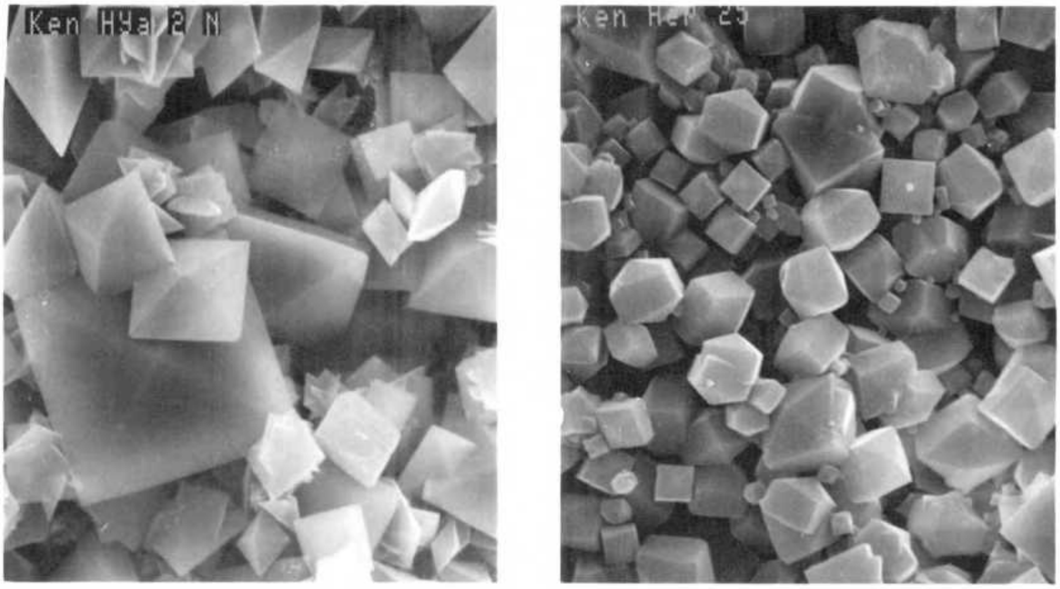
Heparin produces a significant decrease in M_T, a concentration of 10^{-6} mol/l giving a suspension density less than 20% that of the control. Conversely, chondroitin sulphate results in an increase in suspension density by a factor of approximately 2 when present at a concentration of 10^{-6} mol/l. The effect of hyaluronic acid is to increase M_T somewhat at low concentrations but to produce a decrease at concentrations higher than 1.5×10^{-7} mol/l.

Figure 2 contains photomicrographs of representative crystals obtained from some of the experiments. With control conditions, most of the crystals have the morphology of calcium oxalate dihydrate. The addition of chondroitin sulphate at a concentration of 10^{-8} mol/l produces rather more



A Control

B Chondroitin Sulphate
(10^{-8} mol/l)



C Hyaluronic Acid
(10^{-7} mol/l)

D Heparin
(10^{-6} mol/l)

0 10 μm

Fig. 2 Scanning electron photomicrographs of calcium oxalate produced in the presence of different macromolecules.

trihydrate and larger crystals, even at this low concentration. This reflects the increase in crystal growth rate illustrated in Table 2. Hyaluronic acid, at a concentration of 10^{-7} mol/l, also results in larger crystals but with very few trihydrate crystals, the majority being dihydrate. Neither of these GAGs changes the crystal habit (or shape). Heparin, however, has a profound effect on the habit of the dihydrate when present at a concentration of 10^{-6} mol/l. New, apparently cube 100, faces appear and the crystals are significantly smaller, the majority being less than about 6 µm in size. However, the determination of nucleation rate from the plot of log (cumulative crystal number) against crystal size was not affected because the plot was still linear at sizes below 6 µm.

Discussion

The effects of three kinds of glycosaminoglycans on the nucleation rate, growth rate and suspension density of calcium oxalate have been studied and the results may be summarised as follows. Chondroitin sulphate inhibited the nucleation rate and enhanced both the growth rate and suspension density. Hyaluronic acid had a similar effect, although at a concentration of 2.5×10^{-7} mol/l the suspension density was reduced. The inhibitory effect of heparin sodium salt on the nucleation rate and the suspension density was the strongest of the three macromolecules, although it had the weakest effect on the growth rate.

These results differ from the observations of some other workers. Most reports (Robertson *et al.*, 1973; Bowyer *et al.*, 1979; Pak *et al.*, 1979; Ryall *et al.*, 1981) have suggested that heparin and chondroitin sulphate inhibit the growth and aggregation of calcium oxalate crystal formation. It is believed that this difference may have arisen from the different test systems used. In the present study a continuous MSMPR crystalliser system was used. This has several advantages over batch and seeded growth systems (Fleisch, 1985): (i) it operates, and is maintained at, urinary supersaturation levels; (ii) being a flow system, it is a better model of the urinary tract than a batch crystalliser; (iii) any additives are maintained at a constant concentration. Robertson and Scurr (1986) examined the effect of heparin and chondroitin sulphate using a continuous MSMPR crystalliser system. Their results are somewhat different from those of the present study. They showed that these materials enhanced crystal nucleation and inhibited crystal growth. Drach *et al.* (1980, 1982) also examined crystal formation using the continuous MSMPR crystalliser system. They showed inhibition of growth rate and suspension density but promotion of nucleation rate on addition of human urine to synthetic urine. However, Springmann *et al.* (1986) provided different results, namely urine from both normal subjects and those with stones did not affect the growth and suspension density but did decrease the nucleation rate. Furthermore, they showed that urine from stone groups inhibited aggregation. Their recent data concerning nucleation rate are the same as those in the present study. Based on the present findings, and on other results using the continuous MSMPR crystalliser system, there is evidence that different GAGs produce different effects on the nucleation and growth rates of calcium exalate.

Urinary GAGs in normal subjects consist mainly of chondroitin sulphate and small quantities of heparan sulphate, keratan sulphate and hyaluronic acid (Baba *et al.*, 1983). It should be noted that human urine does not contain heparin sodium but rather heparan sulphate. The latter, however, was not available when these experiments were performed. The effect of chondroitin sulphate and heparin on calcium oxalate crystal formation has been studied previously but little work has been done to investigate the effect of hyaluronic acid. The principal GAGs in urinary stones are hyaluronic acid and heparan sulphate (Nishio *et al.*, 1985; Roberts and Resnick, 1986). The most prominent urinary GAG, chondroitin sulphate, is notably absent from urinary stone matrix. On the basis of the present study, there is evidence that hyaluronic acid also influences calcium oxalate stone formation.

The mechanism by which these GAGs influence the crystallisation process has not been specifically addressed in this study. We may speculate that the inhibition of the nucleation rate by all GAGs results from competition with oxalate ions to complex with calcium ions, since GAGs contain a strong anion. The inhibition of the growth rate by heparin may be explained by a similar mechanism. The promotion of growth rate by chondroitin sulphate is not fully explained and further studies into this aspect are necessary. In particular, it is important to evaluate the effect of GAGs on crystal aggregation because the possibility exists that chondroitin sulphate may influence aggregation, resulting in changes in the apparent growth rates.

It is recognised that aggregation is an important contributory process in stone formation. In the present study some aggregates were evident in the

SEM photographs, particularly in Figures 2B and 2C. Such aggregates do not form a significant proportion of the total crystal numbers and, in any case, it is always difficult to determine how many of such aggregates were present in the crystalliser rather than having been formed during filtration, drying and sample preparation. Crystal size distribution always gave a straight line when plotted as log (cumulative number) against size. This was also found in an earlier study (Kohri *et al.*, 1988) and provides further evidence that aggregation did not play a significant role in these experiments. Indeed, one striking feature of Figure 2 is how very few aggregates were observed, particularly when heparin was present (Fig. 2D); here the crystals are overwhelmingly well defined and separate.

In summary, the present work indicates that the influence of glycosaminoglycans on urinary stone formation is complex, with particular glycosaminoglycans having specific effects. Clearly, any attempt to describe the role of glycosaminoglycans in general terms would be a gross oversimplification.

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Radiation Safety during Percutaneous Nephrolithotomy

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Summary—Percutaneous nephrolithotomy entails a potential risk of radiation injury to the surgeon if undertaken regularly. The results of 55 consecutive cases of PCN are presented.

The risks associated with exposure to X-rays are well known and the nature of those risks and methods of reducing them are becoming more widely understood (Kelsey *et al.*, 1984). Most surgeons recognise the need to wear a lead apron during X-ray fluoroscopy procedures and assume that this form of protection is entirely adequate, covering as it does the trunk of the user and usually any radiation dose monitor he may wear. Unfortunately, the hands, arms, head and neck remain unprotected and it is possible for radiation dose limits for these parts to be exceeded before the limit for "whole body" under the apron is approached. All such dose limits are internationally recognised and have legal standing in the UK.

For the urologist undertaking regular percutaneous surgery, there may therefore be some risk of later radiation injury to hands, thyroid and eyes as a result of fluoroscopic screening.

X-ray exposure can arise from primary radiation, *e.g.* if the surgeon's fingers are in the direct X-ray beam either before it enters or after leaving the patient, or from secondary radiation scatter which originates mainly from the patient. Within the direct or primary beam, the X-ray intensity is governed by the inverse square law (intensity proportional to l/distance^2), since the X-rays come from a point source. This is additional to any reduction in intensity due to X-ray attenuation by the patient or the table top. Outside the primary beam, the X-ray intensity falls rapidly, reaching 5% of the primary beam within a few cm and 1% within 1 m of the edge of the beam. The intensity does not obey the inverse square law in this region because the effective "source" is large.

Standard fluoroscopy tables comprise either an overcouch tube with undertable intensifier or an undertable X-ray source with overhead intensifiers. Because of the physical properties of X-rays, these 2 systems are by no means comparable when considering radiation safety for the surgeon.

At the energies of diagnostic X-rays, the intensity of scatter is roughly uniform in all directions. Since the primary X-ray intensity is usually at least 10 times greater at the point where the beam enters the patient than at the point where it leaves the patient, it follows also that scattered radiation must be much greater on the beam entrance side. It can be seen from the diagram (Fig. 1), therefore, that doses to the user (both from primary radiation as well as from scatter) are substantially greater with an overcouch system, such as is found on the widely used Uroskop table, than would occur using an undercouch X-ray source.

For the urologist practising stone surgery, the risk of long-term injury to unprotected parts such as eyes, thyroid or fingers should be reduced by having the X-ray beam coned down to the smallest acceptable size. As scatter is proportional to the area of the beam, coning down reduces both primary and secondary radiation to staff and patient. It has the important additional advantage of improving the quality of the X-ray image. Minimising beam-on time will also reduce dose, as will the use of an undercouch tube or a C-arm mobile tube in the undercouch position.

X-ray doses are reported here for one surgeon using an overcouch X-ray source.

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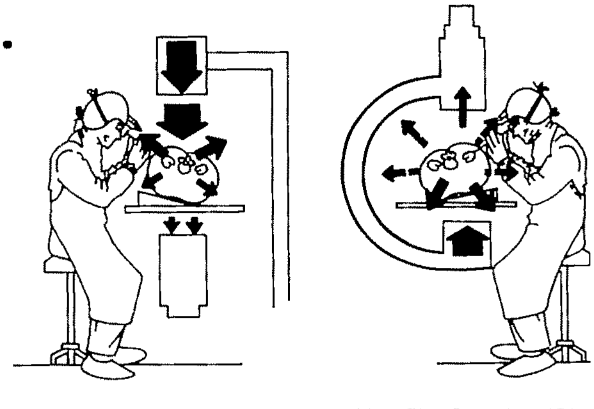

Fig. 1 Comparative radiation danger using overcouch and undercouch tubes

Patients and Methods

A group of 55 consecutive patients undergoing elective percutaneous nephrolithotomy (PCN) was studied. They were unselected regarding size, site and type of stone and included multiple as well as staghorn calculi. All patients underwent single-stage PCN by the same surgeon after prior insertion of a ureteric catheter to facilitate access, the surgeon establishing access to collecting systems as well as retrieving the stone.

During each procedure X-ray exposure was assessed using thermoluminescent dose monitors (TLDs) worn under surgical gloves on the fingers of both hands. During the later part of the study period an additional monitor was worn over the thyroid. The monitors were stored dry and simply placed in Cidex solution 10 min prior to use. They were then applied to the dorsum of the middle phalanges of the ring and index fingers using "Band Aid" type dressings and worn under surgical gloves in the normal way. No significant impairment of surgical dexterity was noted.

The monitors were obtained from the Regional Radiation Physics and Protection Service, Queen Elizabeth Medical Centre, Birmingham. They were renewed every 4 weeks and returned to Birmingham for assessment. Screening time and operative details were carefully recorded for each case; the X-ray tube factors employed were generally 75 to 80 kV and around 1.5 mA.

Results

The results for 55 consecutive patients showed an average screening time of 4.4 min (range 1.2–12.5) per case and this included the establishment of percutaneous access as well as the endoscopic removal of the calculus and insertion of a nephrostomy tube at the end of the procedure. The average radiation dose to the fingers was up to 0.34 mSv per case (Table). The dose per unit screening time remained remarkably constant throughout the study, as did the pattern of exposure to individual digits, the left index receiving most radiation (Law *et al.*, unpublished data). This pattern is predictable for a right-hand surgeon steadying instruments with his left hand during screening and has been described before (Lowe *et al.*, 1986). The radiation dose to the surgeon's eyes/thyroid was less than 0.035 mSv/patient, which is considerably less than the dose to the fingers. In 1 further 4-week period, 4 procedures only were performed and on some of the fingers the dose reported was below the minimum reporting level of 0.2 mSv. If these few results were included, precise averages could not be calculated.

Discussion

In order to view these results in context, it must be remembered that annual dose limits for radiation exposure to fingers and eyes are 500 mSv and 150 mSv respectively; therefore this operator could safely perform almost 30 procedures per week even using the potentially more dangerous overcouch tube.

It should be noted, however, that such apparently reassuring results were obtained only because this experienced operator used minimal screening and kept his hands outwith the main X-ray beam at all times. Results from other series (Bush *et al.*, 1984; Lowe *et al.*, 1986; Rao *et al.*, 1987) showed that even when biplanar screening and memory storage systems were used, screening times of 20 min/patient were not unusual, especially when trainee surgeons were operating. Such screening times using an overcouch system such as ours would limit the number of procedures that could be performed

Table Radiation Doses Received to Fingers of Surgeon over a 6-month Period

Monitoring position	*Total dose (6 months) (mSv)*	*Dose per procedure (μSv)*	*Dose/min (μSv)*
L. middle finger	12 4	226	51
L. index finger	18 8	342	78
R middle finger	5.5	100	23
R. index finger	10 4	189	43

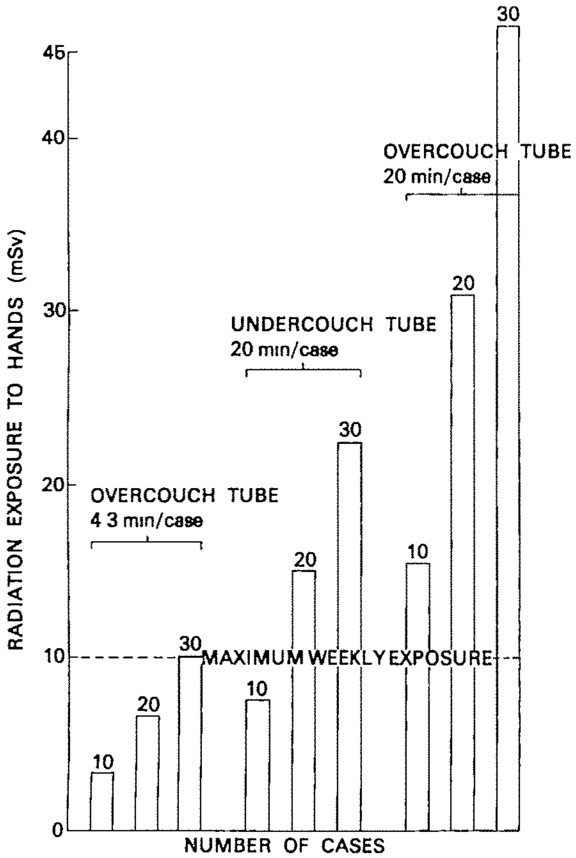

Fig. 2 Permitted weekly workload dependent on operator screening time and type of X-ray source.

without risk of exceeding dose limits to a maximum of 6/week.

Kelsey *et al.* (1984) reported that, using an overcouch tube and with an average screening time of 30 min, the number of their procedures would be limited to 10 *per annum*. Conversely, using an undercouch system a surgeon performing a single-stage procedure with a screening time of 20 min could safely perform 13 procedures/week (Fig. 2).

In November 1987 the National Radiological Protection Board recommended that dose limits in the UK be reduced to $\frac{3}{10}$ of their present levels, though at present the existing dose limits remain in force. Recommendations on possible reductions are still awaited from the International Commission on Radiation Protection, but if this recommendation is accepted, only $\frac{3}{10}$ of the number of cases stated here will be permissible.

The significantly increased risk of radiation exposure using an overcouch system effectively nullifies any imagined practical advantage of a combined lithotripter/endourology table. Our radiation doses are low, despite using an overcouch tube, simply because of very short screening times not generally achieved in other centres.

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Value of the Gamma Camera Renogram in the Differential Diagnosis of Acute Tubular Necrosis and Rejection in the Early Post-transplant Period

Comparison with Biopsy Findings

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Summary—A group of 128 consecutive patients was identified on whom renal isotope studies had been performed during the first 2 months after renal transplantation and within 7 days of transplant biopsy. The prospective renogram and biopsy reports were reviewed and graded into 4 categories: severe rejection, predominant rejection, predominant acute tubular necrosis (ATN) and pure ATN. Two extreme patterns of renogram were identified: a sharp rise with a fast decline in the first min, attributed to ATN, and a slowly rising curve with no early peak occurring in severe rejection although not specific to this condition. There was a continuous intermediate spectrum. There was no inter-observer variation in gradings at the 2 ends of the spectrum. In the middle part the difference between 2 independent observers never exceeded more than 1 grade.

There was good correlation between the biopsy and renogram gradings, with a discrepancy of more than 1 grade in only 5 patients; 2 of these, with severe rejection on the renogram, showed predominant ATN on biopsy, but the final clinical diagnosis was severe rejection (false positive biopsies). Two patients with biopsies showing severe rejection had a sharp initial up-slope in the renograms but a slower down-slope (over 4 min compared with 1 min in true ATN). With better definition of the criteria these renograms would not have been graded as ATN. There was 1 patient in whom no satisfactory explanation for the discrepancy was found (presumed false positive renogram). When properly defined criteria are used to interpret renograms, this simple test is at least as reliable as renal biopsy in differentiating ATN from rejection in the early post-transplant period, especially in the presence of anuria or severe oligurea.

Despite the important therapeutic implications, distinction between acute tubular necrosis and other causes of oliguria or anuria immediately after renal transplantation is often difficult. There is as yet no generally accepted test which gives a precise and accurate diagnosis. Renal biopsy and renograms are performed in the majority of cases, but at the end of the day treatment is usually based on the overall clinical impression. Several studies have suggested that renograms, especially if performed serially, are helpful in diagnosing ATN (Burke *et al.*, 1979; McConnell *et al.*, 1984), although there are some who doubt its accuracy and usefulness in the post-transplant patient (Lancet, 1986). Renal biopsy is invaluable in some cases but since it is invasive it cannot be performed repeatedly and is usually undertaken as a last resort; it is generally accepted as conclusive, but there are no reports in the literature comparing it with renograms or with clinical follow-up. We have looked prospectively at individual renogram patterns and compared them with concurrent biopsy reports in post-transplant patients during their early post-operative course. The 2 tests give very similar results in the majority of patients; neither is infallible and their diagnostic accuracy is not significantly different.

Accepted for publication 20 October 1988

Patients and Methods

All biopsy reports on patients who had undergone renal transplantation in the Nuffield Transplant Unit between 1977 and 1987 were reviewed; 289 biopsies had been performed within the first 2 months following transplantation. In 128 of these a renogram was performed within 7 days of the date of biopsy; 84% of these renograms were within 4 days of the biopsy date (Fig. 1). Where more than 1 renogram had been performed following the biopsy, only the renogram nearest to the date of biopsy was considered for this study. The biopsies were performed using a "Trucut" biopsy needle. The samples were sent for light microscopy, electron microscopy and immunofluorescence studies. For the present study the original biopsy slides were re-examined by a pathologist when there was a discrepancy between the methods, as all are kept indefinitely.

Renogram studies were usually performed using a large-field gamma camera positioned over the supine patient, to include the transplant kidney area. A small number of studies were performed using a small-field camera. 150 MBq (4 mCi) of diethylene-triamino-penta-acetic acid labelled with technetium 99m (^{99m}Tc-DTPA) was given as a bolus injection into an antecubital vein. Data acquisition was immediately started, with 2-s frames for the first 2 min followed by 30-s frames for a total of 15 min. A static late picture (400 K count) was acquired at 30 min. Two regions of interest (ROI) were drawn, one including the transplant kidney area and a second over the contralateral corresponding area of the pelvis for background. Two curves were calculated, one of counts in the background area and the second a background subtracted transplant curve. They are expressed as counts (y axis) against time (x axis) and are not displayed normalised to equal sizes of ROI.

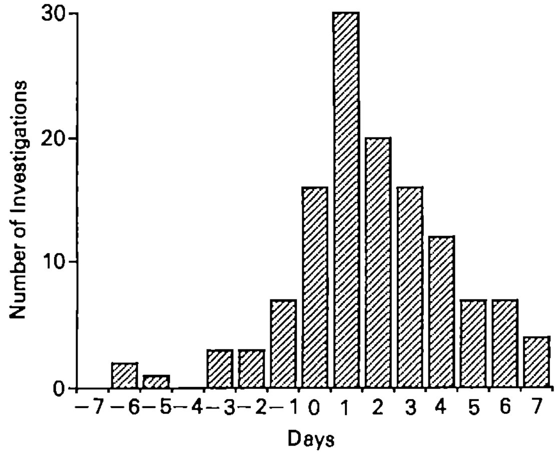


Fig. 1 Number of investigations at 0 to 7 days' interval between renal biopsy and renogram (negative numbers when renogram preceded biopsies; positive numbers are the interval in days when renogram followed biopsy)

Both when reporting prospectively and when reviewing retrospectively, a spectrum of renogram curves was identified. A slowly rising curve for the first 4 to 8 min of the study followed by a slow or absent further rise, representing poor function (Fig. 2), was considered equivalent to the biopsy report of severe rejection (Group 1). This is a non-specific pattern which can also occur with any cause of severely impaired function and in renal artery stenosis. However, the clinical presentation of the latter condition is different, usually presenting at a later date. At the other end of the spectrum, a rapid peak followed by a sharp fall in count rate within the first min of the study, followed by a flat or very slowly rising curve (Fig. 3), was considered indicative of ATN (Group 4). So far as we can ascertain, this pattern has not been described previously in the literature, except in nephrotoxicity due to cortenarius toxins (Merrick, 1984), and may be concealed when longer frame times are employed. The remainder were categorised in the clinical context of early post-operative period as "predominant ATN" or "predominant rejection", depending on the relative extent to which both sets of features were present. For the retrospective part of the study all renograms were reviewed more than 1 year later and graded independently by 2 observers who had no prior knowledge of the original renogram or biopsy report, clinical data or the final outcome of the transplant. Biopsy reports were reviewed and divided into similar categories without the knowledge of the renogram grading for

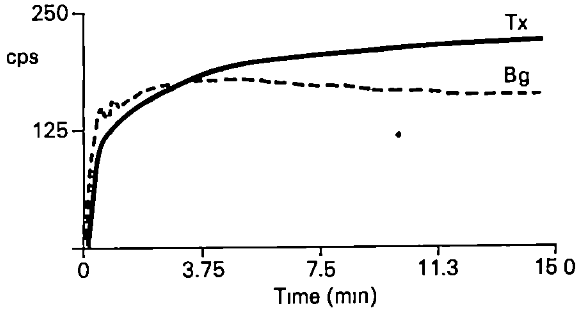


Fig. 2 Typical curve of severe rejection. cps = counts per second. Tx = transplant curve. Bg = background curve.

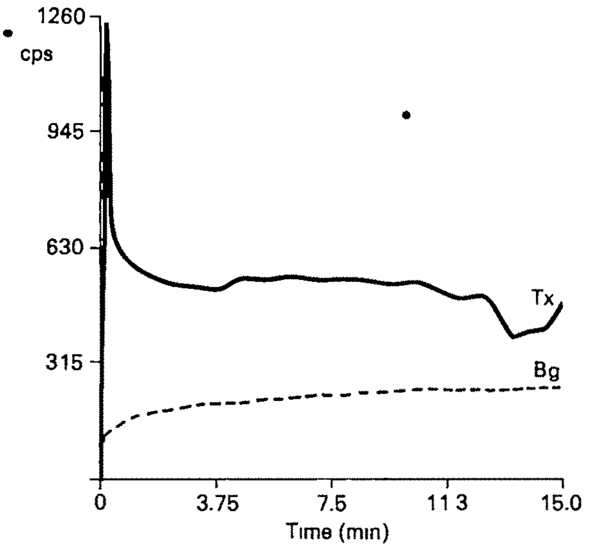


Fig. 3 Typical curve of pure acute tubular necrosis. cps = counts per second Tx = transplant curve. Bg = background curve.

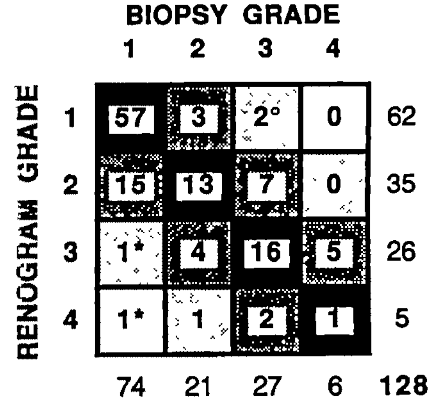
individual patients. As a continuous spectrum of changes was divided into 4 arbitrary groups, there were some intermediate cases which could be included in either of 2 grades. In a pilot study no case was found in which two observers (or the same observer on 2 occasions) differed by more than 1 grade. In 90% of cases there was no disagreement. An observer difference of 1 grade was therefore accepted as non-significant; a difference of more than 1 grade between the 2 methods was considered significant.

Results

In 74 biopsies severe rejection was seen (grade 1); 21 showed predominant rejection (grade 2), 27 predominant ATN (grade 3) and 6 pure ATN (grade 4). There was a similar distribution in renogram gradings with 62 showing severe rejection, 35 predominant rejection, 26 predominant ATN and 5 pure ATN. The results are summarised in Figure 4. There was complete agreement between the 2 diagnostic tests in 87 patients, represented by black squares in Figure 4. A difference of only 1 grade between the biopsy and renogram grading (represented by squares with dark shading in the figure) is within the range of observer error. When this margin of error is included, there were only 5 patients in whom there was a significant difference between the biopsy and renogram grading (a difference of more than 1 grade). Two of these showed severe rejection on biopsy (grade 1) while the renograms were interpreted as having predominant or pure ATN (grades 3 and 4) and in 2 others the biopsy showed predominant ATN (grade 3) whilst the renograms showed severe rejection (grade 1). One patient with predominant rejection on biopsy (grade 2) showed a renogram pattern of pure ATN (grade 4). These cases were reviewed.

Discussion

There is continuing controversy over the value of renograms for the differential diagnosis between rejection and ATN (Delmonico *et al.*, 1977; Hilson, 1986; Lancet, 1986). In this centre, DTPA has been used hitherto for transplant renograms because, in order to identify the early vascular phase, a higher photon flux is necessary than can be achieved with acceptable activities of I131–OIH. I123–OIH, considered by some to be superior, is over 10 times more expensive for an equal photon flux and was available to us on only 1 day per week—useless when a clinical decision is required immediately. Various indices have been proposed for the diagnosis of rejection in post-transplant patients. McConnell *et al.* (1984) found that curve peak calculation, "transit time" and washout of DTPA gave a correct diagnosis of rejection in 47 of 52 patients, whilst the changes preceded the acute episode of rejection in the remainder. They did not report their findings in ATN and this degree of diagnostic precision has not been reproduced elsewhere. Some studies have found the calculation



	BIOPSY GRADE				
RENOGRAM GRADE	1	2	3	4	
1	57	3	2°	0	62
2	15	13	7	0	35
3	1*	4	16	5	26
4	1*	1	2	1	5
	74	21	27	6	128

Fig. 4 Comparison of gradings of renal biopsy reports and renogram curves (1 = severe rejection; 2 = predominant rejection, 3 = predominant ATN; 4 = pure ATN). ° = Both biopsies showed severe ATN, thought to be focal ATN due to extensive rejection * = Unusual renogram curves.

of a perfusion index a useful means of diagnosing rejection (Burke *et al.*, 1979). Hilson *et al.* (1978) found the perfusion index helpful in the diagnosis of rejection if performed serially in the same patient, although renal artery stenosis resulted in perfusion indices indistinguishable from rejection. They did not report their findings in ATN. Some have expressed greater doubts about the value of isotope investigations for the diagnosis of ATN and rejection (Lancet, 1986). There remains no generally accepted rapid method of diagnosing ATN.

Categorising post-transplant patients with deteriorating or absent function into 2 groups, ATN and rejection, is artificial and unrealistic, since these conditions usually coexist. There is in reality a spectrum of findings which at one end is represented by severe rejection and at the other by pure ATN. Patients in this latter category can subsequently develop rejection episodes during or after recovery from the ATN. In our study we could distinguish 2 distinct categories of renograms representing the 2 ends of the spectrum in the early post-transplant period. A sharp rise and a sharp descent of the background subtracted renogram curve within the first minute of a rapid bolus of ^{99m}Tc-DTPA was associated with pure ATN (Fig. 3). All of these patients were oliguric or anuric at the time. This was correctly diagnosed prospectively in all patients in whom ATN was confirmed. There were thus no false negatives, but in both the prospective and the retrospective evaluation there was 1 false positive (the same case). The ATN renogram pattern is due to normal (or possibly increased) blood flow without significant isotope extraction, and thus absence of the rising curve of a normal kidney. These curves are similar to the first-pass activity recorded over an organ with high blood flow but without excretory function, such as aorta or spleen. This preservation of renal blood flow in ATN was observed by Shanahan *et al.* (1981), who looked at the early frames to observe the enhanced "flush" of the transplant kidney in ATN, a finding reproduced in the present series.

A slow rise, tending to plateau after 5 min, was associated with (although not specific for) severe rejection (Fig. 2). This is expected, as rejection affects blood flow into the kidney, with small and medium sized vessels involved in the process (Jackson *et al.*, 1986). We categorised the rest of the renograms according to the degree of prominence of these features into predominant rejection or predominant ATN. Half of the renograms fell into this range of mixed pattern. Both biopsy and subsequent observed course confirmed that these patients had both ATN and rejection, the intermediate pattern correctly indicating dual pathology. These were also correctly diagnosed prospectively.

In all of the studies reviewed the reference diagnostic standard is clinical diagnosis. This is a combination of biochemical investigations, clinical course and, in some cases, biopsy results in post-transplant patients. Since there are no definitive diagnostic criteria, it makes the evaluation of a single technique more difficult (Freedman, 1987). In our study we looked principally to the biopsy results for comparison, as this is generally considered the most consistent diagnostic investigation, usually performed once all other investigations have been inconclusive. However, we have not regarded any single test as definitive; final diagnosis is based on the overall clinical picture. Biopsy is invasive and therefore it is not practical for repeated examination of the patients in the sometimes prolonged post-operative course, although it should serve as a good reference test to evaluate radioisotope investigation. Besides being an invasive test, biopsy has another major drawback which we encountered in 2 of our patients, namely the focal nature of needle biopsy. This can be inadequate for the diagnosis of overall renal pathology. This was appreciated by the pathologist reporting these patients. He was tentative in diagnosing pure ATN in a post-transplant patient who had strong clinical evidence of rejection, as this could be a focal phenomenon distal to an occluded vessel due to rejection. In our 2 patients in whom the renogram was suggestive of rejection while biopsy suggested ATN, the investigations were done 30 and 31 days after transplantation, an interval at which ATN is unlikely to occur. In both patients the final clinical diagnosis was rejection, in agreement with the renogram; they responded appropriately to anti-rejection therapy.

In 2 other patients in whom the renogram was thought on review initially to indicate ATN while biopsy showed predominant rejection, the renograms were re-reviewed. There was a rapid rise of the renogram curve but this, unlike the true ATN shown in Figure 3, was followed by a slow descent, over 4 rather than 1 min (Fig. 5). We now appreciate that this is a non-specific pattern not typical of ATN and in retrospect should not have been categorised into the pure ATN group. Subsequent renograms and the clinical course indicated rejection. In 1 patient no definite explanation could be found for the inaccurate diagnosis of pure ATN by renogram while the biopsy and subsequent clinical

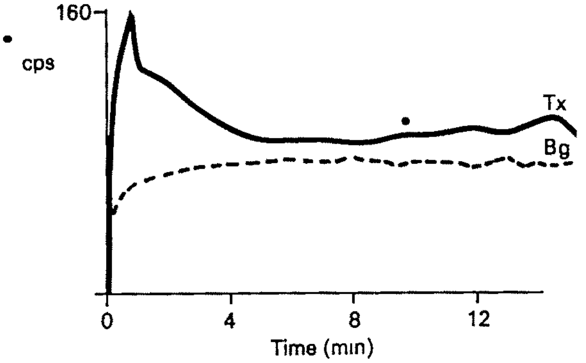


Fig. 5 Atypical renogram curve misdiagnosed as ATN in the initial assessment of renograms but to be distinguished from ATN renogram curve by slower downslope.

course indicated predominant rejection. The most likely explanation is misplacement of regions of interest in a poorly functioning kidney which was difficult to visualise. This was exacerbated by the use of a small-field camera which excluded most of the usual landmarks. It should, however, be pointed out that this patient had 4 consecutive renograms after the biopsy. Although the first renograms on the day of biopsy indicated ATN, the rest of the renograms, performed 3 days apart, which were disregarded for this study as they were not the nearest to biopsy date, showed predominant and severe rejection. It is also possible that the biopsy was taken from a small area of rejection while the overall function had not yet deteriorated. Even so, when clinical criteria are used as the end point, the overall accuracy of the renogram studies was 125 of 128 renograms reviewed (98%). With a clearer definition of the criteria of diagnosing ATN an accuracy of 127/128 (99%) was achievable. The renal biopsies gave the correct diagnosis in 126 of 128 biopsies (98%). This indicates that the accuracy of the renogram is comparable with that of renal biopsy.

With the use of cyclosporin there is now a new dimension to the problem of diagnosing post-transplant renal failure, namely cyclosporin toxicity. In our series of concurrent renograms and biopsies there were only 2 patients whose biopsies suggested cyclosporin toxicity, but there was also a suggestion of rejection in these patients. There was no specific pattern of renogram in these cases, the renograms having the same non-specific pattern as is found in predominant rejection. In theory, cyclosporin might mimic ATN, for cyclosporin toxicity mainly affects the tubules, although it has also been suggested that cyclosporin toxicity could reduce blood flow to transplant kidneys (Thomsen *et al.*, 1987). More work is indicated in patients receiving cyclosporin to evaluate the effect of this drug on the renogram pattern.

Because biopsies, in our centre, are mainly restricted to patients with progressive renal failure or anuria with no clear clinical diagnosis, all of our biopsies were performed on abnormal kidneys. The renogram pattern described appears to be a rapid and relatively accurate method of diagnosing ATN. The false positive that we encountered could have been (and was) corrected by follow-up studies and did not affect the outcome. Thus our conclusions are valid in the early post-operative period in patients with progressive renal failure or anuria. As has been stressed in several studies (Burke *et al.*, 1979, McConnell *et al.*, 1984), serial examination of renal function with DTPA can add to its diagnostic value, indicating a trend in the changes of renogram patterns, possibly before they are clinically expressed and thus enabling earlier intervention to prevent full blown rejection.

Other causes of transplant oliguria such as infarction, ureteric obstruction or leakage from the ureteric anastomosis, are not diagnosed by biopsy and thus are not included in the present series. These conditions are not associated with characteristic curves but in our experience can readily be diagnosed by inspection of all of the images obtained during the renogram.

Since completing this survey we have observed 2 further patients with confirmed ATN whom we examined with both DTPA and MAG3 (mercapto-actyl-triglycine). Both showed the characteristic pattern we described with DTPA, but non-specific rising curves with MAG3. We interpret this as suggesting that the uptake of MAG3 is unaffected in ATN, but it is not secreted into the lumen of the renal tubules. A similar phenomenon is said to occur with 123I–IOH, although we have not been able to trace any published report of this.

In conclusion, this study indicates that when these defined criteria are used to interpret renograms in the early post-operative period, this simple test can differentiate ATN from rejection as reliably as renal biopsy, with the advantage of repeatability and with no additional risk to the patients. However, because of the small risk of a false positive, the examination should be repeated 24 h later if the study suggests ATN.

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Nephrectomy in Renal Carcinoma with Distant Metastasis

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Summary—A total of 96 cases of renal carcinoma with distant metastasis at the time of diagnosis was studied. The patients were classified into 4 groups: Group O (16) in whom nephrectomy was not performed, Group A (51) who died due to carcinoma within 1 year of nephrectomy, Group B (25) who died due to carcinoma 1 to 3 years after nephrectomy, and Group C (4) who survived for 3 years or more after nephrectomy.

Six clinical measurements were evaluated: haemoglobin, ESR, α_2 globulin, temperature, weight and C reactive protein. In addition, performance status, the number of organs with metastases, number of metastatic lesions and tumour growth rate were measured.

The results showed that in patients surviving for 1 year or more after nephrectomy, there was an abnormality in the results of 3 or less of the 6 clinical measurements, performance was 0 or 1, and the carcinoma had metastasised to only one organ. In addition, it was found that the growth of metastatic lesions in patients who survived for 3 years or more was much slower than in the other patients. Nephrectomy was found to be effective in only 27% of our cases and we consider that careful deliberation should be made pre-operatively as to whether nephrectomy is really necessary in patients with metastasis. The decision should be made on the basis of the results obtained in the 6 clinical measurements given above.

In patients with renal carcinoma, nephrectomy is the procedure of choice. However, distant metastasis is detected at the time of the first medical examination in approximately 30% of patients presenting with this disease (Middleton, 1967). In some of these cases nephrectomy does not necessarily improve prognosis (Klugo *et al.*, 1977). We investigated the indications for, and clinical significance of, nephrectomy in 96 patients with renal carcinoma with distant metastasis at the time of diagnosis.

Patients and Methods

Distant metastasis of renal carcinoma was detected at the time of initial diagnosis in 110 of 397 patients (27.7%) treated at the Jikei University Hospital and its related institutions between January 1957 and December 1984. Four cases of death (3.6%) from intercurrent disease, and 10 cases of surgical mortality (9.1%) were excluded from the study. The remaining 96 patients were studied and the significance of nephrectomy was investigated, mainly in the 80 cases where the primary lesion had been excised.

The age of the patients when renal carcinoma was detected ranged from 22 to 79 years (average 60.4). There were 78 males and 18 females (4.3:1). The primary lesion was in the right kidney in 47 cases and in the left kidney in 49: 80 of the 96 patients with metastasis underwent nephrectomy. The excised kidneys were classified on the basis of histological malignancy into 1 of the following 4 grades: grade I (5 cases, 6.3%), grade II (17 cases, 21.3%), grade III (33 cases, 41.3%), grade IV (25 cases, 31.1%).

The 16 patients who did not undergo nephrec-

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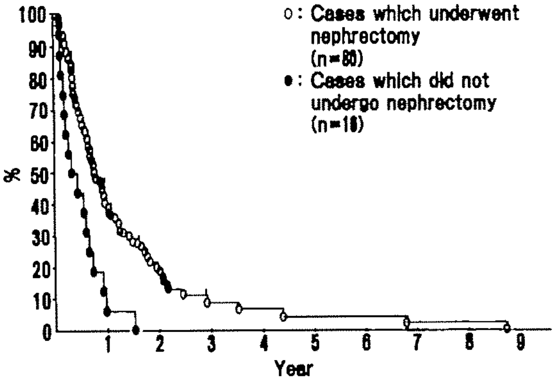

Fig. 1 Survival rates in patients who underwent nephrectomy and those who did not.

Table 1 Pre-operative Performance Status

PS grade	*PS score*	*Condition*
0	1	Able to carry out all normal activity without restriction.
1	2	Restricted in physically strenuous activity but ambulatory and able to carry out light work.
2	3	Ambulatory and capable of all self-care but unable to carry out any work, up and about more than 50% of waking hours.
3	4	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours.
4	5	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

tomy served as a comparative group (Group O). However, the survival rate of nephrectomy patients was higher (Fig. 1); 51 patients died within 1 year of nephrectomy and were designated as Group A. It was considered that surgery did not serve to prolong life in these cases. A total of 25 patients survived for more than 1 year but less than 3 years and 4 survived for more than 3 years. They were designated as Groups B and C respectively. In each of these groups the pre-operative clinical measurements were analysed with respect to the following criteria and an attempt was made to establish indications for nephrectomy in renal carcinoma associated with distant metastasis:

(i) Results of clinical examination at the time of diagnosis. Any abnormalities in the following 6 items were investigated: (1) anaemia (Hb below 10 g/dl); (2) elevation of erythrocyte sedimentation rate (over 30 mm/h); (3) alpha-2-globulin increase; (4) fever (over 37°C); (5) weight loss; (6) positive reaction to C-reactive protein (CRP).

(ii) Pre-operative performance status (PS): distribution of PS scores were compared among the groups (Table 1).

(iii) Number of organs with metastasis and number of metastatic lesions: metastasis was scored in each case (metastasis score) and the average value in each group was calculated from the sum of metastasis scores. Metastases were scored as follows: one organ with 1 to 3 metastatic lesions (1 point); one organ with 4 or more metastatic lesions (2 points); two organs with metastases (3 points); three organs with metastases (4 points); 4 or more organs with metastases (multiple metastases) (5 points).

(iv) Investigation of tumour growth rate in patients who survived for 3 years or more after nephrectomy (Group C). A calculation of tumour doubling time was made (in terms of 2-dimensional measurement) of metastatic lesions which could be evaluated radiologically and the results were compared with those obtained in Group B.

The degree of malignancy was divided into four grades (Bannayan and Lamm, 1970). The survival rates were calculated by Kaplan-Meier's method and were analysed by the generalised Wilcoxon test. Mean differences and rate differences were analysed by the Z test. Performance status (PS) was evaluated according to the Eastern Cooperative Oncology Group (ECOG) criteria. However, score 1 in the scheme employed in the current study was equivalent to score 0 in the PS evaluation method and score 2 to PS score 1. The highest score 5 in our study was equivalent to PS score 4 (Table 1).

Results

The results at clinical examination at the time of the initial consultation were as follows:

(1) Anaemia was detected in 30 patients (58.8%) in Group A and 6 (24%) in Group B. The incidence of anaemia in Group A was significantly higher ($z=2.8547$, confidence coefficient $=2.3263$, $P<0.01$).

(2) Elevation of ESR was observed in 14 patients (87.5%) in Group O and 2 (50%) in Group C. The difference was statistically significant ($z=1.6771$, confidence coefficient $=1.6448$, $P<0.05$).

(3) There was no significant difference in the

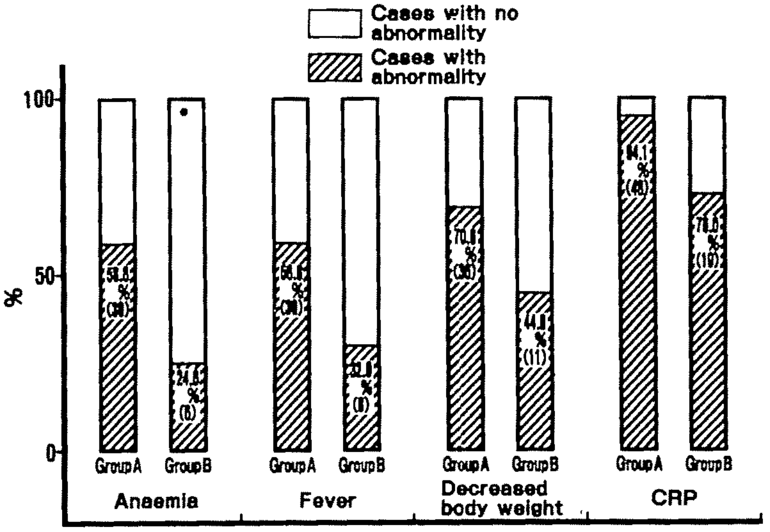

Fig. 2 Incidence of abnormality in results of clinical examinations in Group B (survived for 1 year or more after nephrectomy) and Group A (died less than 1 year after nephrectomy)

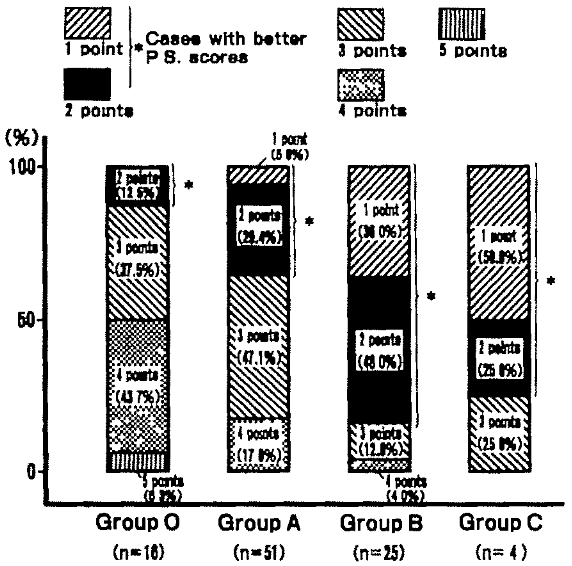

Fig. 3 Distribution of pre-operative performance status scores in each group

number of patients with elevation of alpha-2-globulin among the groups.

(4) Fever was noted in 30 patients (58.8%) in Group A and 8 (32%) in Group B. The difference was significant (z = 2.1954, confidence coefficient = (1.8422, $P < 0.05$).

(5) Body weight loss was observed in 36 patients (70.6%) in Group A and 11 (44%) in Group B. The difference was significant (z = 2.2429, confidence coefficient = 2.2993, $P < 0.01$).

(6) Positive reaction to the CRP test was detected in 48 patients (94.1%) in Group A and 19 (76%) in Group B, indicating a significant difference (Fig. 2) (z = 2.2935, confidence coefficient = 2.3552, $P < 0.05$).

On the basis of these results, the average number of items in which abnormality was detected and comparison of the averages were calculated among the groups (Fig. 2). It was found that the number of items in which abnormality was observed in Group A was significantly larger than in Group B. Elevation of ESR, fever, body weight loss and a positive CRP test reaction were particularly important factors.

In those patients who died within 1 year of nephrectomy the results of the clinical examination were poor, showing gross abnormality in 4 or more of the 6 examination items. On the other hand, in most of the patients who survived for more than 1 year after nephrectomy, the number of items in which abnormality was detected was 3 or less (Table 2).

The distribution of pre-operative performance status classified by group was summarised. The average PS score in Group O was 3.44 and the scores in Groups A, B and C were 2.76, 1,84 and 1.75 respectively. There was a significant difference in the score between Groups A and B (Fig. 3) (z = 4.7052, confidence coefficient = 3.2906, $P < 0.001$).

As a result, it was found that in most of the

Table 2 Comparison of Average Number of Examination Items with Abnormal Results among Groups (total number of examination items was 6)

	Group O (n=16)	*Group A (n=51)*	*Group B (n=25)*	*Group C (n=4)*
M±S.D.	5.19±0.75	4.78±1.34	2.85±1.41*	2.75±2.36

* Significantly different
{*Z=5.7688, Confidence coefficient=2.8070, ($P<0.001$)}

patients who died within a year of nephrectomy, the PS score was 3 or 4, equivalent to 2 or 3 according to the ECOG scoring scheme. These patients were unable to perform even light work (Table 1, Fig. 3).

The group averages of metastasis were 4.00, 3.92, 2.92 and 2.75 in Groups O, A, B and C respectively and there was a significant difference in the group average of metastasis score between Groups A and B. In view of this, it was considered that prolongation of life for more than 1 year after nephrectomy could be expected only in patients with metastasis scores of 3 or less, *i.e.* with metastasis limited to a single organ (Fig. 4).

The average tumour doubling time in metastatic lesions, particularly in the lung fields, was calculated in Groups B and C. The doubling time was 4.68 ± 1.79 months in Group B and 7.95 ± 2.56 months in Group C, and there was therefore a significant difference between the two groups ($z=2.4662$, confidence coefficient$=1.9600$, $P<0.05$).

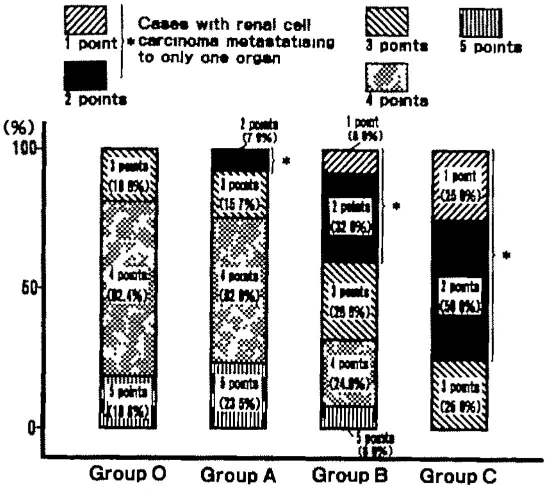

Fig. 4 Distribution of metastasis scores among groups.

Discussion

In the field of clinical oncology there has been a great improvement in prognosis during the last 10 years, and the number of patients in whom renal carcinoma is diagnosed at a relatively early stage has been increasing (Johnson *et al.*, 1985). Even now, however, many patients are first diagnosed when they have distant metastasis and their treatment has been discussed from many aspects.

In this hospital we have adopted the basic therapeutic guidelines which give preference to removing the kidney with the primary lesion, whenever feasible, even in renal carcinoma with distant metastasis. Some investigators oppose nephrectomy in these cases (Johnson *et al.*, 1975).

Generally speaking, the prognosis is relatively poor in renal carcinoma patients with distant metastases at initial diagnosis, and death due to carcinoma occurred within 1 year in about 65% of our patients. Of these, 51 (52.4%) were patients who died within 1 year of nephrectomy. It is difficult to suggest that nephrectomy was of value in these cases and it is considered that the indication for nephrectomy in cases of renal carcinoma with distant metastasis should be defined more strictly.

To date, nephrectomy has been performed in renal carcinoma with distant metastasis in order to improve local symptoms such as pain and haematuria, because spontaneous regression of metastatic lesions has sometimes been noted after nephrectomy, or because judgment was coloured by the emotions of the patient and the attending physicians, who felt that surgery was immediately necessary (Middleton, 1967).

It is now possible to treat the primary lesion in patients with a poor performance score by means of trans-catheter embolisation without nephrectomy (Lang and deKernion, 1981). In addition, spontaneous regression of the metastatic focus after nephrectomy is unlikely (the incidence of such spontaneous regression is as low as 0.8%) (deKernion *et al.*, 1978). In view of this, it has become increasingly difficult to justify nephrectomy in renal carcinoma with distant metastasis and it is effective in only about 5 to 15% of cases. It is therefore considered that the grounds used in this department to justify nephrectomy are no longer tenable. However, some nephrectomy patients survived for 1 year or more and where factors likely to prolong survival exist, nephrectomy may be considered advantageous. We have attempted to analyse various factors in order to find criteria upon which the indication for nephrectomy can be based. Pre-operative clinical findings such as ESR elevation, CRP positive reaction, increase in alpha-2-globulin, anaemia, fever and weight loss are considered important indices which indicate the exhaustion of carcinoma-bearing hosts, although not specific to renal disease (Bowman and Martinez, 1968; Aftaffer and Chenault, 1979).

Survival for more than 1 year is unlikely in patients who show abnormalities in 4 or more of the 6 clinical measurements and in these cases the decision to perform nephrectomy should be made very carefully. Our analysis also shows that nephrectomy is indicated for patients with a PS score less than 2.

Although there are various conditions which justify nephrectomy in renal carcinoma with distant metastasis, Middleton (1967) studied the treatment of metastatic lesion in 141 stage 4B cases and concluded that it was effective only where there was metastasis to a single organ. We report similar findings. However, satisfactory results cannot be expected in patients where the single metastasised organ is the brain, particularly in the area adjacent to the brain stem, because it is difficult to excise such lesions. However, the prognosis is good in cases where the metastasis is to bone, regardless of the number of metastatic lesions, and nephrectomy is advisable in patients with one or more bony metastases (Johnson *et al.*, 1975; Montie *et al.*, 1977).

In the current study, 4 patients survived for 3 years or more. The pre-operative clinical characteristics, based on the results obtained in the 6 clinical measurements in these cases, included the following: abnormality in 3 of the 6 items, average PS score less than 2, and average metastases score 2.8. Thus the general condition in these 4 patients was better than in the others. In addition, those patients in whom the tumour doubling time of lung metastases was very long survived for 3 years or more. In these patients, excision of the metastatic lesion is recommended.

Ten patients (9.1%) who died within 1 month of nephrectomy were excluded from our analysis. It has been reported that the surgical mortality rate for patients without metastasis was 2.3 to 11% (Johnson *et al.*, 1975; Montie *et al.*, 1977; deKernion *et al.*, 1978). These 10 patients were not a small number in comparison with the total number of stage 4B patients. More precise investigation showed that 3 had very large renal tumours, over 1 kg in weight, accompanied by 5000 ml or more blood loss during operation. In these cases death followed 2 to 18 days after nephrectomy. Another 5 patients who died 18 to 26 days after surgery were in poor physical condition. Of the remaining 2 patients, 1 died during operation from malignant hyperthermia; the other underwent gastrectomy for stress-induced gastric bleeding and died as a result of disseminated intravascular coagulation.

It is considered that nephrectomy should not be carried out routinely in patients with metastasis at the time of diagnosis unless systemic adjuvant therapy, effective against renal carcinoma, is available. The physician should also consider the patient's quality of life and treat accordingly.

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Clinical Application of Transrectal Ultrasound for the Investigation of the Incontinent Patient

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Summary—A transrectal ultrasound technique is described for imaging the bladder neck and urethra. A group of 25 continent female volunteers was examined initially; 59 incontinent women were then studied pre-operatively and again 6 months after either a Burch colposuspension, Pereyra operation or ox fascial sling to determine the ultrasonic characteristics of successful surgery.

No single investigation can provide all of the information needed in the assessment of the incontinent patient. Instead, a combination of tests is necessary.

X-ray cystography has been the most frequently used imaging technique and when coupled with synchronous pressure-flow measurements becomes an extremely comprehensive investigation. An alternative to X-ray imaging is ultrasound. Holmes (1967) used a transabdominal approach, but the symphysis pubis often obscured the view of the urethrovesical junction. A transrectal probe which was initially developed to study the prostate (Watanabe *et al.*, 1974) has more recently been used to study the bladder and urethra (Nishizawa *et al.*, 1982; Brown *et al.*, 1983; Perkash and Friedland, 1983; Shapeero *et al.*, 1983; Richmond *et al.*, 1984; Brown *et al.*, 1985; Richmond *et al.*, 1986).

In this study we used linear array real-time ultrasound and a transrectal probe to demonstrate the dynamic relationships of the bladder, urethra and symphysis pubis during stress. Two groups of patients were studied: 25 continent volunteers and 59 consecutive incontinent female patients admitted for surgery. In the latter group 3 different operations were assessed in the pre-operative and post-operative phases.

Patients and Methods

That the 25 volunteers were all continent of urine was confirmed by history, clinical examination, a perineal padweighing test and transrectal scanning. They did not undergo urodynamic investigation. Their mean age was 39 years and parity 3. The second group of 59 incontinent female patients (mean age 49 years, range 25–73; mean parity 3, range 0–10) included 20 who had already undergone surgical procedures, most of which were vaginal repairs. All of these patients underwent a standard series of investigations comprising perineal padweighing test, urine flowmetry, supine and provocative medium—fill water cystometry, a urethral pressure profile measurement and fluid bridge testing. Transrectal ultrasound was used to screen the bladder at rest, during a series of coughs and bearing down manoeuvres in the erect and supine positions. The images were recorded on videotape. Using a single freeze frame technique, polaroid pictures were taken of the resting and maximum straining positions of the bladder and urethra in relation to the symphysis pubis.

Each patient acted as her own control. The symphysis pubis was used as the reference point. Although the angle of inclination and width of the symphysis vary from patient to patient, they remain constant for each individual and can therefore be used as a template for comparison of the resting and straining images.

From each polaroid picture the following meas-

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urements were made: the midline of the symphysis was obtained by drawing a line between 3 points equidistant from the anterior and posterior surfaces; this was extended to bisect the urethra. A further line was drawn along the proximal 1 cm of the urethra and extended to meet the symphysis axis line. By drawing a vertical tangent at the junction of the axis line and the bony shadow of the symphysis, the angle A or bearing of the bladder neck in degrees of a clockwise arc could be measured. Angle B was the urethral angle of the proximal 1 cm of urethra in degrees clockwise from the vertical (Fig. 1).

The posterior urethrovesical angle (angle C) was measured between the proximal urethral line and the flat portion of the bladder base immediately posterior to the internal urethral meatus. Angle D corresponded to the angle in a clockwise arc subtended by the axis line and its vertical at the junction with the symphysis (Fig. 2).

Three distances were measured (in cm). X was the distance from the symphysis to the internal urethral meatus, Y was the distance from the symphysis to the urethra along the axis line and Z was the distance from the internal urethral meatus to the junction with the extended symphysis axis line (Fig. 3). Seven measurements were therefore available for comparison.

Results

Continent patients

There was no statistically significant difference between the resting and straining positions for distance Y (from symphysis to urethra along the axis line) and angle D (the angle of the symphysis). However, significant results were obtained for the remaining 5 variables between the resting and straining images for each patient (Table 1).

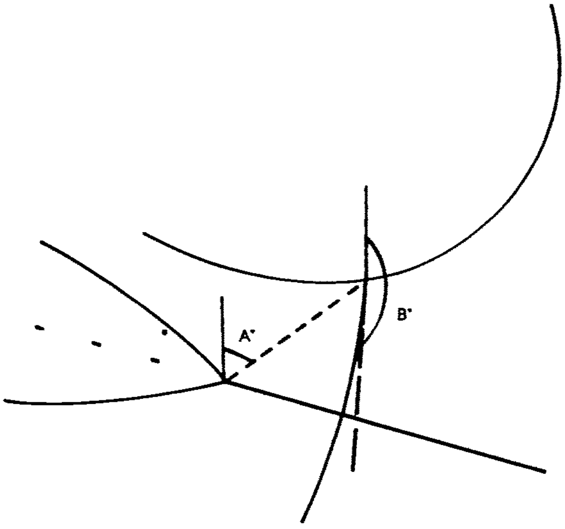

Fig. 1 Measurement of angles A and B

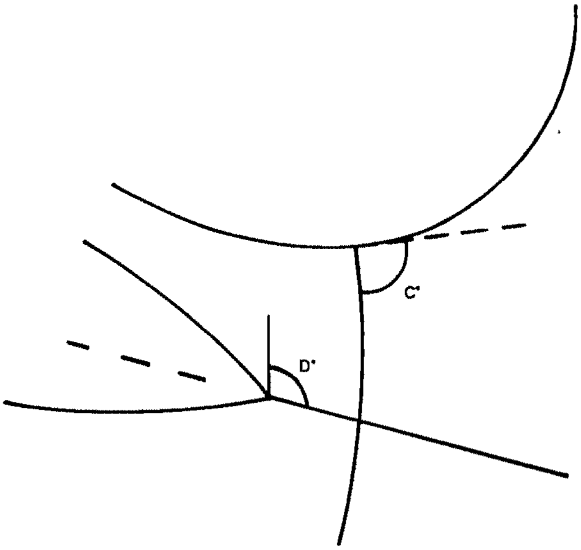

Fig. 2 Measurement of angles C and D

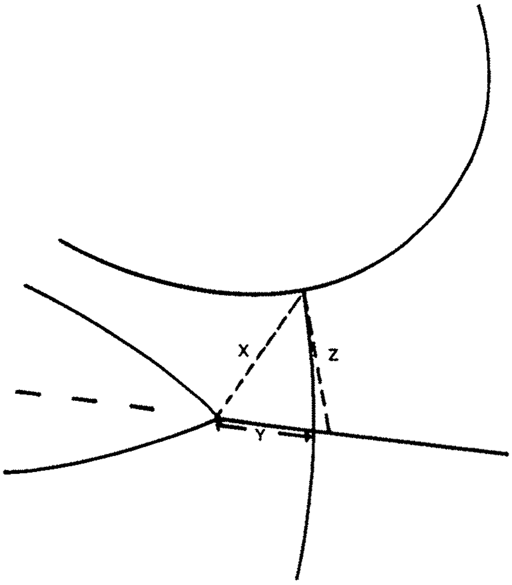

Fig. 3 Measurement of distances X, Y and Z.

For this series, *i.e.* normal patients, the bladder neck was seen to descend (Z) by a mean of 1 cm and the bladder neck bearing increased by a mean of 28.8°.

Table 1 Difference in Resting and Straining Mean Values in 25 Control Patients

Variable	*Difference Straining/ Resting*	*T*	*P*
X	−0.3	2.29	0.008*
Y	−0.01	0.09	0.928
Z	−1.0	9.40	0.000†
A	28.8	−7.18	0.000†
B	17.3	6.20	0.000†
C	16.2	−4.71	0.000†
D	0.1	−0.31	0.893

*0.001 < P < 0.01
†P < 0.001.

Incontinent patients (pre-operative investigation)

The method for measuring the 7 variables was the same as for the continent patients. A comparison of the 2 groups at rest and straining is shown in Figure 4.

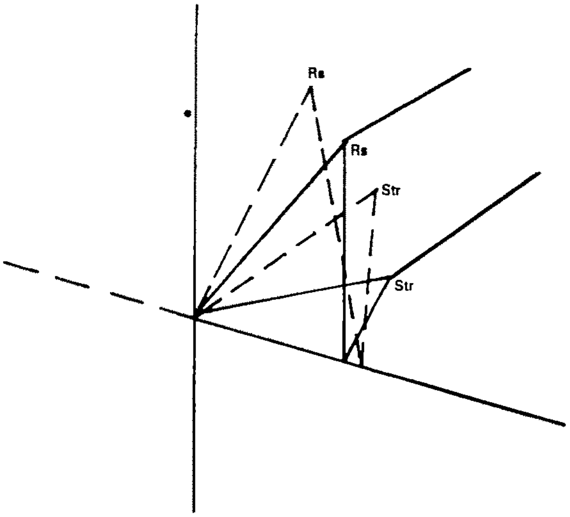

Fig. 4 Diagram of mean bladder neck movement during stress before surgery. ------ Continent volunteer patients. ——— Incontinent patients. Rs: resting position. Str: straining position.

Incontinent patients (post-operative investigation)

In 19 patients a Burch colposuspension was performed; 23 had a Pereyra suspension and 17 an ox fascial sling; 34 were completely cured according to our subjective and objective criteria (stable filling and provocative cystometry with a padtest < 1 ml/h); 5 patients were symptomatically cured but leaked 1 to 2 ml/h during padtesting.

Three patients had post-operative detrusor instability; 13 of the Burch patients (77%) were continent, 13 of the Pereyra patients (59%) were cured but only 8 of the sling patients (47%) were continent. However, these tended to be secondary procedures for recurrent incontinence, where the expected success rate is lower. In addition, 3 sling patients had stable bladders and cough-competent bladder neck mechanism on urethral stress testing, with leakage only on exercising.

Thus 70% of patients were either cured or dramatically improved by objective testing and 84% were subjectively better.

The resting/straining relationships for the successful and unsuccessful operations are shown in Figure 5.

Statistically significant results were observed for the successful operations only (Table 2).

Discussion

Women with stress incontinence experience a leakage of urine when the bladder pressure rises

Table 2 Difference between Pre-operative and Post-operative Resting/Straining Values in Continent Patients according to Operation

Variable	*Mean difference (Burch)*	*P*	*Mean difference (Pereyra)*	*P*	*Mean difference (Sling)*	*P*
X	0.1	0.46	0.0	0.79	0.2	0.18
Y	0.3	0.36	0.3	0.18	0.1	0.32
Z	0	0.02*	0.8	0.018*	0.9	0.08
A	25.6	0.018*	25.0	0.026*	32.9	0.025*
B	15.0	0.005†	15.5	0.15	35.6	0.002†
C	14.5	0.14	0.1	0.99	50.0	0.001‡
D	2.1	0.43	0.4	0.93	3.1	0.542

*0.01 < P < 0.05
†0.001 < P < 0.01
‡P < 0.001.

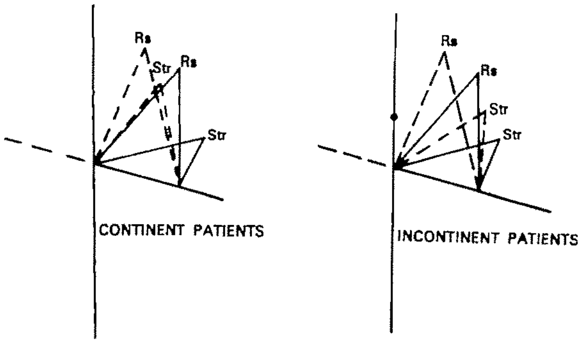

Fig. 5 Diagram of resting/straining positions after surgery. ------ Continent patients ———— Incontinent patients.

and overcomes the urethral resistance. This is usually due to a failure of adequate pressure transmission to the proximal urethra either because of descent and rotation of the bladder neck or damage to the integrity of the components which normally keep the urethra closed, *i.e.* vascular, neuromuscular and connective tissue elements. Parturition is said to be a major contributory factor as a result of pudendal and perineal nerve damage (Smith and Warrell, 1984; Snooks and Swash, 1984) and also vaginal surgery. In particular, any bladder neck surgery causes scar tissue formation which may interfere with pressure transmission.

In this study we assessed bladder neck mobility and its relation to stress incontinence. By comparing the pre- and post-operative positions we hoped to show a significant difference between successful and unsuccessful operations.

The continent volunteers demonstrated that descent and posterior rotation of the bladder neck were normal occurrences in parous patients. Incontinent women, however, usually demonstrated greater bladder neck mobility. In a few cases the urethrovesical junction appeared to be "fixed" and urine loss was presumably due to inadequate pressure transmission as a result of periurethral fibrosis.

Significant differences were seen in the continent group only (distance Z; measuring descent/rotation and angles A, B and C). There was no difference for angle D (axis of the symphysis) for any of the operations irrespective of the outcome. In successful Burch colposuspension procedures significant changes were observed for Z, A and B. The length X was unchanged. Forward angulation of the urethra (along an arc length of X) would therefore increase length Z and decrease lengths A and B accordingly. Success of the Burch operation therefore seems to depend upon this angulation and in particular its maintenance during stress. In 4 cases where the operation failed there were only minimal differences between the pre-operative rest/strain changes and the measurements after surgery, none of which was statistically significant. In this small group the bladder neck was already elevated and further surgery using a Burch colposuspension was unlikely to succeed. The reason for the incontinence remains unclear but may be related to periurethral fibrosis in the presence of a low urethral closure pressure. This group should probably be treated by urethrolysis and the implantation of an artificial urinary sphincter.

The successful Pereyra procedures showed changes for length Z and angle A only. It appears that the mechanism of cure was similar to that of the Burch operation.

Statistically significant differences were observed for the successful sling operations by comparing the stress positions after surgery. Continence was achieved by reducing mobility of the bladder neck, the sling preventing descent and therefore maintaining the proximal urethra within the abdominal pressure transmission zone. In the incontinent sling patients there was inadequate support either because the bladder neck required elevation in the first place or because the sling tension was inadequate. A simple loose platform at the base of the bladder is therefore insufficient.

It was our practice to perform a Burch colposuspension as first-line therapy, reserving the Pereyra procedure for the obese, older and more infirm patient and using the ox fascial sling as a second line of defence. We have conducted a prospective study to select the operation based on the preoperative ultrasound appearance of the bladder neck during stress. Incontinent patients with a relatively fixed bladder neck now have a Burch colposuspension and those with descent and rotation are treated with a sling procedure.

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Intravesical Bacillus Calmette-Guérin Treatment for Superficial Bladder Tumours

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Summary—Intravesical instillations of Tokyo 172 strain BCG were given to 56 patients with superficial bladder cancer during the 24-month period after transurethral tumour resection as a prophylaxis against tumour recurrence. The recurrence rate of tumours was compared with that of historical controls. Results were estimated by the person-years method and there were statistically significant decreases in recurrent tumours following BCG therapy.

Our results suggest that the intravesical Tokyo 172 strain BCG is effective and safe as a prophylaxis against the recurrence of superficial bladder tumours.

Approximately 80% of bladder tumours are superficial at the time of diagnosis (Silverberg, 1979). Current standard therapy for superficial bladder cancer is transurethral resection with cystoscopic and cytological follow-up (Soloway, 1983). However, reports show that patients with resected superficial bladder tumours have a recurrence rate of 40 to 85% (Lum, 1983). Furthermore, most tumours recur within 2 years of the initial treatment (Utz and De Weerd, 1978).

The problem that has confronted us is the prevention of tumour recurrence after resection. Although many different intravesical adjuvant chemotherapeutic regimens for prevention of tumour recurrence have been used, none has yet been considered ideal. Since intravesical BCG therapy for superficial bladder cancer was introduced by Morales *et al.* (1976), it has attracted considerable attention as one of the most effective adjuvant therapies of this type (Haaff *et al.*, 1985).

We present the results of our initial experience with the use of Tokyo strain Bacillus Calmette-Guérin (BCG)* in the prophylaxis of superficial bladder cancer.

Patients and Methods

Two groups of patients were considered to be candidates for intravesical BCG therapy. Group 1 consisted of 19 high risk patients with a history of at least 1 tumour recurrence before BCG therapy. Most had received various forms of intravesical adjuvant chemotherapy (*e.g.* thiotepa, doxorubicin, mitomycin C, cytosine arabinoside) as prophylaxis following previous transurethral resection. The patients' mean age was 67.8 years. The mean follow-up after BCG therapy was 19.7 months (range 6.4–24). Group 2 consisted of 37 consecutive new patients. Their mean age was 65.0 years. The mean follow-up time was 13.2 months (range of 2.1–24). All 56 patients received transurethral resection and/or fulguration of bladder cancer in the 7 days preceding BCG therapy. Independent biopsies from apparently normal mucosa were taken at the time of the initial evaluation. Group 2 contained 5 patients with papillary tumour associated with carcinoma *in situ*.

Results were estimated by simple recurrence rate and by the modified person-years method (Schoenberg and Myers, 1977) during the 2 years following BCG therapy. In group 1, the tumour recurrence rate of patients was compared with the rate during the 2 years prior to BCG therapy as a personal historical control. In group 2, the tumour recurrence rate after BCG therapy was compared with that of historical controls in our hospital. There were 89 other patients who had previously been treated by transurethral resection and most had also received intravesical chemotherapy. Their mean age was

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64.6 years. The mean follow-up after the first treatment was 18.4 months. The total number of control patients was 89, of whom 34 had 58 episodes of tumour recurrence during the 2 years following treatment of the first bladder cancer.

The patients were catheterised, the bladder was emptied and 80 mg lyophilised Tokyo 172 strain BCG (Nihon BCG Co., Japan; the Tokyo strain was derived from the Pasteur strain in 1925), suspended in 40 ml saline and containing 50 to 120×10^6 colony-forming units/mg, were injected into the bladder. The patients were instructed to retain the drug for 2 h. Treatment was given weekly for 6 weeks. The patients were then followed-up with urinary cytology, cystoscopy and cup bladder biopsy every 3 months. The purified protein derivative (PPD) skin test was performed before and after a 6-week course of intravesical BCG.

Results

The case histories of 19 patients in group 1, 24 months before and after BCG therapy, are shown in Figure 1. Patients in this group had at least 1 recurrent tumour during the 24 months preceding BCG therapy and were considered to be at high risk of further recurrence. There were 48 episodes of tumour development in 384.2 patient-months during the 24 months before BCG therapy. After treatment there were 9 episodes (7 patients) of tumour recurrence in 351.1 patient-months. The recurrence rate was compared with that before and after BCG therapy (Table 1). The simple recurrence rate was 36.8% after therapy. According to the person-years method, the number of recurrent tumours per patient-months was 0.125 before and 0.026 after BCG therapy. This demonstrated a statistically significant decrease in recurrent tumours following BCG therapy ($P < 0.01$).

Group 2 comprised 37 patients who presented with bladder tumours for the first time and who received transurethral resection followed by BCG therapy (Fig. 2). Seven of these patients had 9 episodes of tumour recurrence in 489.4 patient-

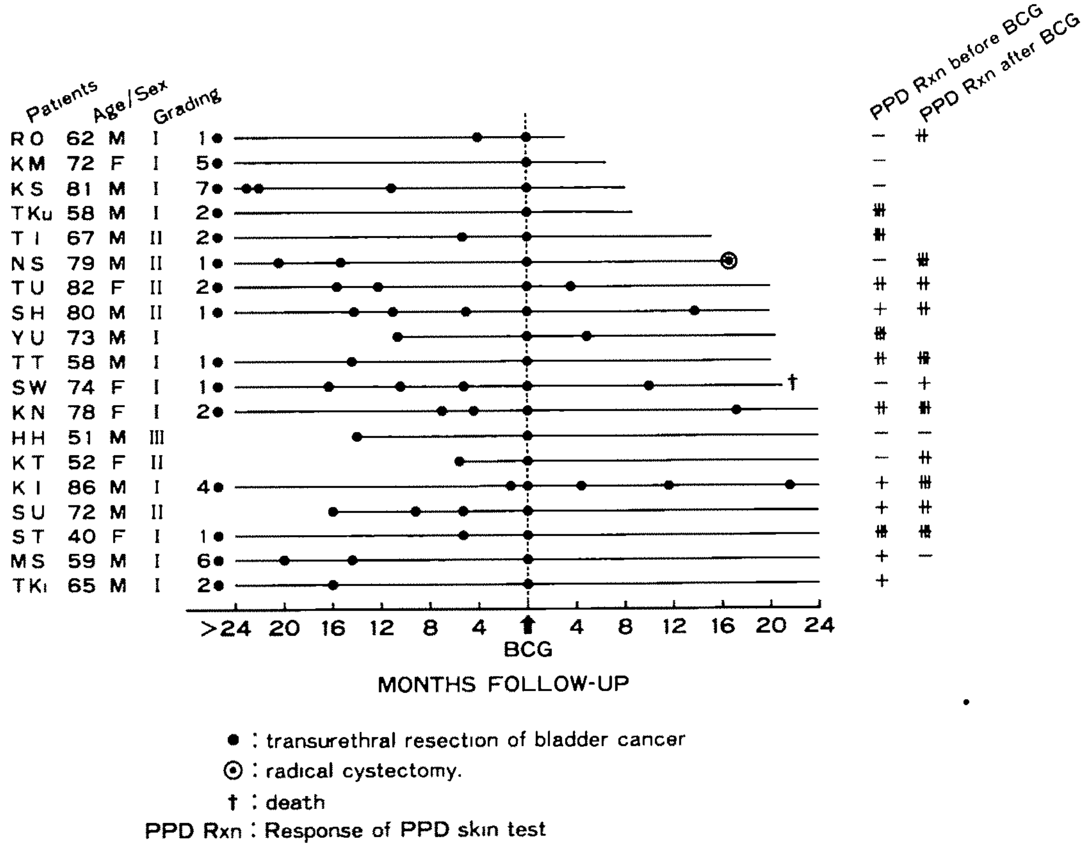

Fig. 1 Clinical history of patients with recurrent bladder tumours 24 months before and after BCG therapy. Purified protein derivative skin reactivities (PPD Rxn) before and after each 6-week course of treatment are shown on the right. One patient (SW-74-F) died of an unrelated cause.

Table 1 Summary of Recurrence Rate in 19 Patients (Group 1) in the 24 Months before and after BCG Therapy

	Simple recurrence rate			
	No of patients	*No of patients with recurrent tumour*	*Recurrence rate (%)*	
	19	7	36.8	
	Person-years method			
	Total no of recurrences	*Total no. of patient-months*	*No of recurrences/ patient-months*	*O/E*
After BCG	9	351.1	0.026**	0.205
Before BCG	48	384.2	0.125	/

**$P<0.01$

O: Number of recurrences following BCG

E. Expected value = (recurrence rate in control) × (patient-months of BCG patients).

months. This recurrence rate was compared with that of the historical control group without BCG therapy (Table 2). The simple recurrence rate was 18.9% in BCG patients and 38.2% in the historical controls. Statistically, this was a significant decrease ($P<0.02$). According to the person-years method, the number of recurrences per patient-months in this group was 0.018. On the other hand, the historical group showed 58 recurrences in 1602.6 patient-months and the number of recurrences per patient-months was 0.036. This difference was also statistically significant ($P<0.05$).

Before intravesical BCG therapy, 16 of 56 patients (28.6%) had a negative PPD skin test, of whom 11 had the PPD skin test following a 6-week course of BCG treatment. The skin test converted to positive following BCG therapy in 9 of 11 patients (81.1%), of whom 3 subsequently developed recurrent tumours. No relationship between PPD responsiveness and the tumour recurrence rate could be detected (Table 3).

More than half of the patients complained of voiding symptoms after BCG therapy (Table 4). Granulomatous prostatitis was seen in 4 patients

Table 2 Summary of Recurrence Rate in 37 Patients (Group 2) in the 24 Months after BCG Therapy and Comparison with Historical Controls

	Simple recurrence rate			
	No. of patients	*No. of patients with recurrent tumour*	*Recurrence rate (%)*	
BCG patients	37	7	18.9*	
Historical control	89	34	38.2	
	Person-years method			
	Total no of recurrences	*Total no of patient-months*	*No of recurrences patient-months*	*O/E*
BCG patients	9	489.4	0.018*	0.511
Historical controls	58	1602.6	0.036	/

*$P<0.02$

**$P<0.05$

O: Number of recurrences following BCG

E: Expected value = (recurrence rate in control) × (patient-months of BCG patients)

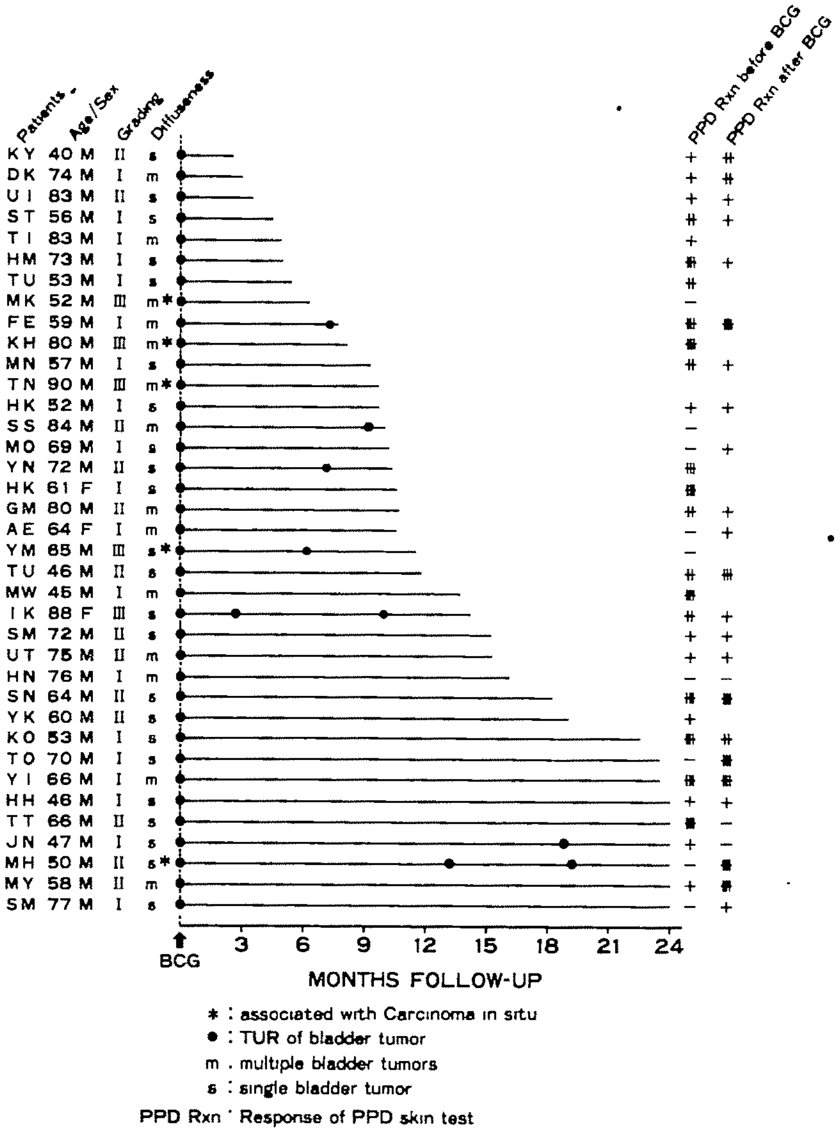

Fig. 2 Clinical course of patients with bladder tumour (first occurrence) for 24 months after BCG therapy. Purified protein derivative skin reactivities (PPD Rxn) before and after each 6-week course of treatment are shown on the right.

Table 3 Relationship between PPD Skin Test and Tumour Recurrence Rate

	No of patients (%)	*No. of patients with recurrence (%)*
Non-sensitised patients	16 (28 6)	5 (31.3)
Conversion (pos.)	9	3
No conversion (neg.)	2	0
PPD skin test not done after BCG	5	2
Previously sensitised patients	39 (69.6)	9 (23.1)
PPD skin test not done before BCG	1 (1.8)	
Total	56 (100 0)	

Table 4 Correlation of Side Effects with PPD Skin Reactivity before BCG

		Pre-BCG skin test	
	No. of patients (%)	*Positive (%)*	*Negative (%)*
Vesical irritability	34 (54.0)	25 (55.6)	9 (50.0)
High grade fever	5 (7.9)	4 (9.3)	1 (5.6)
Macrohaematuria	5 (7.9)	3 (6.7)	2 (11.1)
Granulomatous prostatitis	4 (6.3)	4 (8.9)	0 (0)
Urethralgia	1 (1.6)	1 (2.2)	0 (0)
Negligible symptoms	14 (22.2)	8 (17-8)	6 (33.3)
Total	63 (100)	45 (100)	18 (100)

and although these were asymptomatic, except for 1 patient with urinary difficulty, needle biopsy was required to distinguish granulomatous prostatitis from tumour invasion into the prostatic gland in 2 patients. There were no significant side effects or fatal complications attributable to BCG therapy in this series. Only 3 patients had to stop the treatment because of side effects (high grade fever and vesical irritability). The PPD skin reactivity did not correlate with side effects (Orihuela *et al.*, 1987).

Discussion

Most studies involving intravesical BCG therapy for superficial bladder cancer have supported its efficacy. The recurrence rate is 10 to 20% for BCG-treated patients compared with 40 to 85% for conventional treatments such as intravesical chemotherapy and resection alone (Haaff *et al.*, 1985). Various strains of BCG were used and it was reported that all were effective as a prophylaxis and in treatment for superficial bladder cancer. Although previous reports showed that only the Glaxo strain was less effective (Hersh *et al.*, 1976), the efficacy of a new type of Glaxo BCG was recently reported without serious side effects (El-Demiry *et al.*, 1987; Kaisary, 1987). Our results suggest that the intravesical Tokyo strain BCG is also effective as a prophylaxis against the recurrence of superficial bladder tumours. Although a correlation between the PPD skin test conversion and favourable results has been observed (Kelley *et al.*, 1985; Lamm *et al.*, 1985), we could not detect this in our series. It would appear that one explanation for this is the low number of patients not already sensitised before BCG therapy. Most Japanese schoolchildren receive vaccination against tuberculosis. In Japan, therefore, the PPD negative response before BCG therapy may imply that the patient has lost the delayed type hypersensitivity due either to age or to the presence of an advanced tumour.

The mechanisms of BCG toxicity are not well understood, although side effects are common (Lamm *et al.*, 1986). It is also known that the intensity of the side effects depends on the immunological competence of the patient. The rare severe or fatal complications of BCG have occurred almost exclusively in immunosuppressed patients (Sparks *et al.*, 1973). By way of contrast, severe side effects have appeared as a severe hypersensitivity reaction (Orihuela *et al.*, 1987). We were concerned that our patients might have serious complications for the latter reason, because the majority (69.6%) were previously sensitised by BCG vaccine. A strong secondary immunological local response was therefore predicted. However, there were no significant side effects or fatal complications of BCG therapy during the observation period.

In conclusion, our results suggest that the Tokyo 172 strain BCG is effective and relatively safe as a prophylaxis against the recurrence of superficial bladder tumours.

Acknowledgments

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CA–50 as Tumour Marker in Transitional Bladder Carcinoma

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Summary—Monoclonal antibody CA–50 is a useful tumour marker in gastrointestinal carcinoma. We report an assessment of its value in bladder cancer patients. We found raised levels in 2 of 2 patients with infiltrating carcinoma and in 8 of 35 with superficial carcinoma. The recurrence rate was higher in patients with raised levels, since 6 of 8 with elevated levels and 15 of 27 with normal values had a recurrence within 6 months. T1 and T3 carcinoma had a mean CA–50 level higher than normal. G3 tumours had a mean level slightly above normal. A statistically significant difference emerged when comparing Ta with T1+T3 carcinomas. A longer study, with serial determinations, could assess the role of CA–50 as a prognostic indicator in bladder cancer.

Tumour markers, whether oncofetal or tissue-associated antigens, hormones or enzymes, have been described for a variety of malignancies. Tests using antisera against such markers are of limited diagnostic value, primarily because of the unacceptably high rate of false positives, especially among patients with benign disease. Nevertheless, assays for turmour markers, such as CEA, alpha-fetoprotein and choriogonadotrophin, are useful as non-invasive tests in monitoring cancer patients to detect tumour recurrence or to assess the effects of therapy.

Monoclonal antibody technology has provided the means to develop improved methods for the definition and quantification of tumour markers. Monoclonal antibodies with reported specificity for several major classes of tumours have been developed.

A mouse monoclonal antibody, C–50 MAb, has been obtained after immunisation with a human colorectal adenocarcinoma cell line Colo 205. The C–50 MAb recognises 2 different carbohydrate structures, sialylated Lewis-a and sialylated lacto-N-tetratose. The CA–50 antigens exist in the cell membrane in a lipid-bound form, ganglioside, and in a high molecular weight protein-bound form, glycoprotein, which has been named CanAg. The CA–50 antigens have been detected in carcinomas of many organs (Holmgren *et al.*, 1984). The CA–50-containing antigens are shed from the tumour into the circulation, where they can be specifically determined by immunometric assay using C–50 MAb.

Patients and Methods

Serum CA–50 levels were determined in 37 patients, 32 males and 5 females, with histologically proven bladder carcinoma. A complete grading and staging classification, according to UICC (1978), is shown in the Table.

All patients were newly diagnosed and serum was taken immediately before treatment. Serum samples were stored at −20°C before analysis. All analyses were performed in duplicate using the immunoradiometric assay kit (Stena Diagnostic, Gothenburg, Sweden). The CanAg CA–50 IRMA

Table Classification of Grade and Stage

	G1	*G2*	*G3*	*Total*
TA	12	15	0	27
T1	0	4	4	8
T3	0	0	2	2
Total	12	19	6	37

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is a solid-phase immunoradiometric assay based on the sandwich technique. The solid-phase C–50 MAb, immobilised on polystyrene beads, reacts with CA–50 antigenic sites. After washing, the bound CA–50 antigen is detected following 3 hours' incubation with ^{125}I labelled C–50 MAb.

After additional washing, the tubes are transferred to a gamma scintillation counter. The bound radioactivity is proportional to the CA–50 concentration.

The upper limit of the normal range for CA–50 was set at 23 u/ml, as the mean ±2.5 SD obtained from a series of 200 healthy controls (blood donors and hospital staff); this value has been used in previous gastroenterological studies (Pecchio *et al.*, 1987). This upper limit of the normal range is higher than the one proposed by Holmgren *et al.* (1984), but we think that the 17 u/ml they suggested could lead to confusion in concomitant inflammatory diseases (Pecchio *et al.*, 1987). The CV of our assay was $<10\%$.

Results

In 10 of 37 patients (27%), the levels of CA–50 were greater than 23 u/ml; 1 of these patients had invasive and anaplastic disease, pT3G3N+. She underwent a total cystectomy with a colon conduit and died 9 months later. Another patient, without lymph node involvement, received a total cystectomy with the same type of urinary diversion. He was clinically disease-free after 8 months.

Three patients had a pT1G2 carcinoma. They were treated by transurethral resection (TUR) and after 6 months 1 of them had a histologically proven recurrence with an increase in grade. Five patients had a pTa tumour with G1 or G2 grading. They were all treated by TUR; 3 of them had a superficial recurrence after 6 months. In 27 patients the CA–50 values were normal. These included 22 with a pTa (10 pTaG1, 12 pTaG2) and 5 with a pT1 carcinoma (1 pT1G2, 4 pT1G3). All were treated by TUR. Eleven of 22 patients with a pTa, and 4 of 5 with pT1 carcinoma, had a recurrence in 6 months (Fig.).

Statistical analysis was performed by categorising patients according to their stage and grade and by combining T1+T3 and G2+G3 groups. T3 and G3 groups were too small to be considered separately. In the Ta group the mean CA–50 level was within the normal range, 16.79 u/ml. In the T1 and T3 groups the mean CA–50 levels were raised, 31.15 and 40.15 u/ml respectively. Since the distribution of values was not normal the statistical analysis was performed with a non-parametric test. We used the Kruskal-Wallis one-way analysis of variance for ranked data and a significant P was calculated between Ta versus T1+T3 carcinomas ($P=0.003$).

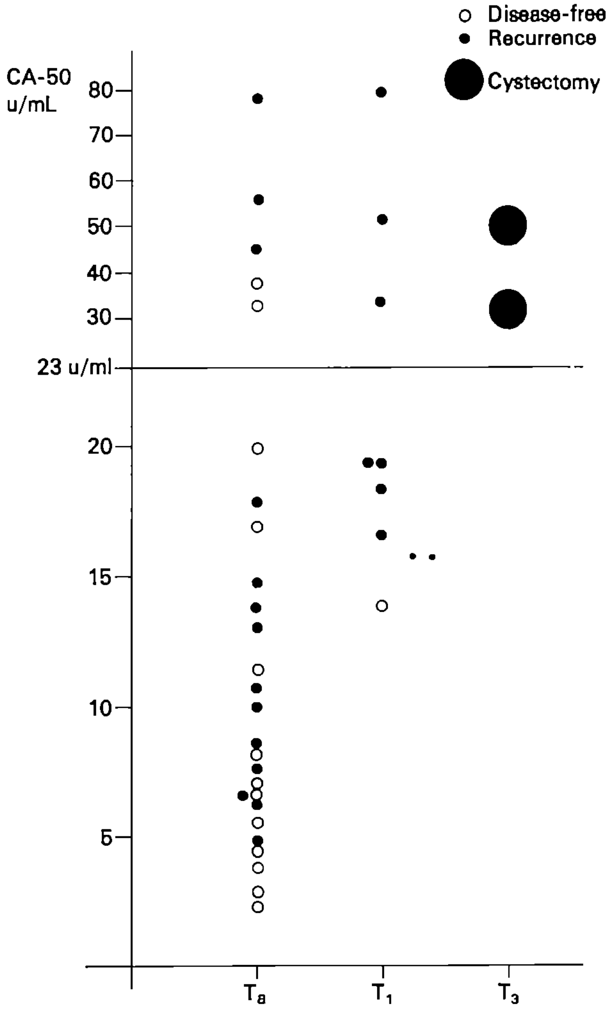

Fig. CA–50 serum levels.

In G1 tumours the mean CA–50 level was also within normal limits, 14.97 u/ml; G2 and G3 tumour levels were 23.66 and 25.62 u/ml respectively.

Discussion

CA–50 is of established value in the treatment of pancreatic and gastrointestinal carcinoma (Paganuzzi *et al.*, 1985; Habib *et al.*, 1986).

This study reports the measurement of serum CA–50 in bladder cancer. Of 37 patients, 10 had raised CA–50 values; 2 of them had invasive and 6 superficial disease. The 27 patients with normal values all had superficial carcinoma.

Six of 8 patients with elevated values and 15 of 27 with normal values underwent a TUR and had a recurrence within 6 months. Statistical analysis demonstrated that patients with T1 and T3 tumours had a mean CA–50 level higher than normal. A significant statistical difference existed between Ta and T1+T3 carcinomas. The G1 mean value was within normal limits, G2 and G3 slightly above. Cacciatore *et al.* (1986) reported 25 patients with bladder carcinoma followed up with serial CA–50 determinations for 1 year; 21 had raised levels, of whom 5 had a recurrence within 1 year, with CA–50 values invariably positive; 16 patients were disease-free but only 2 had normal CA–50 values. The cut-off value was set by these authors at 10 u/ml.

CA–50 obviously cannot be used as a screening test in bladder cancer, as we find that patients with high levels have a significantly higher recurrence rate. A longer study with serial determination of CA–50 could determine the value of this marker as a prognostic indictor.

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Voiding Pattern, Urinary Volume, Composition and Bacterial Contamination in Patients with Urinary Diversion via a Continent Ileal Reservoir

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Summary—A series of 41 patients with a continent ileal reservoir for urinary diversion (Kock pouch) was studied with regard to voiding pattern (voiding frequency), voided volume, urinary composition, bacterial contamination and mucus secretion. The mean voiding frequency in 21 patients was 5/24 h and the time required for the procedure, including the time to cover the stoma with a bandage, was 3 to 5 min; 2 patients voided once or twice at night, while 19 patients never did so. The mean volume voided during the day were significantly smaller than the volume voided in the morning. The total 24-h urinary volume exceeded that of normal individuals but the 24-h secretion of electrolytes was within normal limits. Bacterial contamination was found in most samples of urine. Evacuation was not impeded by the rich mucus content of the urine and mucus production did not diminish with time.

Surgically created intestinal reservoirs are used increasingly for urinary bladder augmentation, for replacement of the bladder after cystectomy and for urinary diversion. Exposure to urine leads to an exchange of water and solutes across the intestinal mucosa due to active absorption and to osmotic and concentration gradients. Such shifts of water and solutes may cause metabolic disturbances, particularly in patients with impaired renal function (Ferris and Odel, 1950; Boyce and Vest, 1952; Burnham and Farrer, 1960; Creevy, 1960; Castro and Ram, 1970; Koch and McDougal, 1985). The exchanges of water and solutes may also alter the volume and composition of urine stored in the reservoir.

In reservoirs constructed from a segment of ileum, remarkable morphological changes take place in the mucosa following exposure to urine (Philipson *et al.*, 1987). Complete mucosal atrophy is noted in certain areas of the reservoir, whilst in others short and broad villi still remain. In addition, the enzymatic activity of the brush border disappears. These mucosal changes have been shown to be accompanied by a decrease in the transport capacity of the mucous membrane (Sinatra and Weinberg, 1958; Kollias *et al.*, 1984; Åkerlund and Nilsson, 1986; Åkerlund *et al.*, 1989). In contrast, the caecal mucosa has been reported to be morphologically unchanged after exposure to urine (Bjersing, 1963; Månsson, 1984; Murray *et al.*, 1987). It was therefore considered of interest to study whether the urine output and urine content of electrolytes in patients with urinary diversion via a continent ileal reservoir differed from the output and content in normal individuals and in patients with caecal reservoirs.

The aim of this study was to collect detailed data regarding voiding pattern, voided volume, urinary composition (electrolytes, osmolality, pH), mucus secretion and bacterial contamination in patients with urinary diversion via a continent ileal reservoir.

Patients and Methods

Forty-one patients with urinary diversion via a continent ileal reservoir were studied. All were in good health and the function of the reservoirs was

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satisfactory. The competence of the anti-reflex valve was tested in all patients by radiography. The number of patients participating in each part of the study is given below.

Voiding pattern and electrolyte contents

A group of 21 patents (13 female and 8 males, aged 27–70 years) with a mean post-operative observation time of 3.5 years (range 1–10) registered the times when they emptied the reservoir and measured the volumes emptied over seven 24-h periods. They collected the data during their usual daily activities (at home, at work, *etc*) and with their usual intake of food and fluid. Samples were collected from the patients' first void in the morning, and from 1 void in the afternoon, for determination of the concentrations of sodium, potassium (flame photometry, Investigation laboratory), chloride (spectrophotometry, Greiner), osmolality (freezing point depression, Knauer osmometer) and pH (pH-meter, Radiometer).

Mucus secretion

In 41 patients with varying post-operative time intervals, urine from two 24-h periods was collected for determination of the amount of mucus; 33 patients were examined on more than one occasion and no patient participated more than 4 times. After complete mixing, 2 urine samples of 50 ml were centrifuged at 5000 rev/min for 20 min; the wet weight of the centrifugate was determined and the amount of mucus for the 24-h periods was calculated.

Bacteriology

In 34 patients (25 females and 9 males, aged 21–70 years) with a post-operative observation time ranging from 0.5 to 10 years (mean 3.6), urine samples were taken on several occasions directly from the reservoir and sent for routine bacteriological culture (Drigalsky and azid-sorbitol agar plates). The mean number of cultures per patient was 12.3 (range 3–33). Cultures containing 10^5 bacteria/ml or more were considered positive.

Student's *t* test was used for statistical comparison and a probability value of less than 5% was considered significant.

Results

Voiding pattern

The majority of patients voided their reservoirs 4 to 6 times during a 24-h period (Table 1) and the mean number of voids was 5 (range 3.6–7.3). While 19 of the 21 patients never emptied during the night, 2 preferred to do so. It took 3 to 5 min to evacuate the reservoir, including the time to apply a covering bandage over the stoma. Irrigation was not regarded as necessary for adequate emptying.

Table 1 Mean Number of Voids during seven 24-h Periods

Mean no. of voids	*No. of patients*
Day	
3–4	1
4–5	7
5–6	11
6–7	2
Total	21
Night	
0	19
1–2	2
Total	21

The volume emptied in the morning was 581 ± 167 ml (mean ± SD) and the volume emptied during the day was 422 ± 132 ml (Table 2). The difference was statistically significant ($P < 0.01$). The collected 24-h volume for the 21 patients was 2216 ± 561 ml. The largest portion was usually emptied in the morning. Volumes emptied during the day were 73% of the volume of the morning portions (mean values).

Electrolyte content and mucus

Table 3 shows the values for morning and afternoon urine samples with regard to concentration of electrolytes, pH and osmolality as well as the total 24-h secretion of electrolytes and osmoles. There were no significant differences between morning and afternoon urine. In addition, the amount of mucus in the urine was stable during a post-operative time interval of 6 years (Table 4).

Bacteriology

No patient had constantly negative urine cultures from the reservoir but 7 of the 34 patients had constantly positive cultures (Table 5). In 27 patients, 50% or more of the cultures were positive. Gram

Table 2 Voiding Volumes in 21 Patients during seven 24-h Periods

	Volumes voided (ml) (mean ± SD)
Morning	581 ± 167
Daytime	422 ± 132
Total volume over 24 h	2216 ± 561

Table 3 Concentration of Na+, K+, Cl−, pH and Osmolality in Urinary Samples Collected in the Morning and in the Afternoon (The lower panel shows the total output of electrolytes and osmoles during 24-h: mean ± SD)

	Morning	*Afternoon*
Na^+, mmol/l	61±15	56±16
K^+, mmol/l	36±13	35±15
Cl^-, mmol/l	59±20	55±21
pH	6.4±0.4	6.3±0.5
Osmolality, mOsm/kg	400±54	391±68
	Output/24-h	
Na^+, mmol	129±45	
K^+, mmol	79±27	
Cl^-, mmol	127±51	
Osmoles, mOsm	880±265	

Table 4 Mucus Content in Urine Collected during two 24-h Periods

Postoperative time interval	*No of patients*	*Wet weight/24-h (g) (mean ± SD)*
1–2 months	19	24.3± 7.9
3–4 months	19	30.3±17.0
1 year	12	29.3±23.6
2 years	10	23.0± 7.1
3 years	7	34.4±15.8
4 years	5	28.1± 8.5
5 years	5	29.9±20.0
6 years	7	27.1± 7.7

Table 5 Urinary Cultures from 34 Patients

	No of patients
Constantly negative	0
Constantly positive	7
≥50% of the cultures positive	27
<50% of the cultures positive	7

negative bacteria (*e.g. Escherichia coli, Klebsiella* and *Proteus*) predominated.

Discussion

When patients leave the hospital they are instructed to empty the reservoir at least 4 to 5 times every 24 h and more often if they feel the reservoir to be full. After a short time they adapt to a voiding routine suitable to their daily activities.

The voiding frequency in healthy individuals has not been subject to extensive studies, although Larsson (1988) reported a micturition frequency of 5.9/24 h (range 3–11) in healthy women. In view of these figures, patients with urinary diversion via a continent ileal reservoir, with an evacuation frequency of 5/24 h, seem to have convenient voiding routine. All were satisfied with their regime, especially those who had previously experienced other types of urinary diversion. The 2 patients who voided once or twice during the night did so habitually and not because of discomfort.

The maximum capacity of the ileal reservoir has been reported to be approximately 700 ml (Berglund *et al.*, 1987). In the present investigation the volume of voided urine during the day was approximately 70% of the maximum capacity, while the volume emptied in the morning was close to the maximum capacity. These findings indicate that expansion of the reservoir takes place during the night during the longest interval between evacuations.

Detailed data on the volume and composition of urine from patients with urinary diversion to various types of intestinal reservoirs have been infrequently reported to date. In 11 patients with urinary diversion via caecal reservoirs, the mean urinary output was 1830 ml (Månsson, 1984). In 5 patients whose bladder was replaced by a tubular segment of the ascending colon, output was 2908 ml (McDougal, 1986) and in our series of 21 patients the output was 2216 ml. These figures suggest that the total 24-h urinary output in patients with intestinal urinary reservoirs exceeds that of normal individuals.

In healthy individuals the amount of electrolytes and osmoles excreted in the urine over 24 h is dependent on diet. With a normal diet of 1 g protein/kg body weight and avoiding excessive intake of salt, the 24-h output is 50 to 150 mmol of Na^+ and K^+, 100 to 200 mmol of Cl^- and of osmoles about 600 mOsm. The electrolytes excreted by our patients with urinary diversion via a continent ileal reservoir were within normal limits. The somewhat low concentration of electrolytes and the low osmolality were due to the exchange of water and electrolytes across the reservoir mucosa, but an increased volume of urine compensated for this.

Patients in the present study were instructed to use a clean (but not necessarily sterile) catheter for emptying. This could be one reason for the high frequency of positive urinary cultures. The role of bacterial growth in urine diverted to intestinal segments is still in dispute. In patients with ileal conduits, bacteriuria has been reported to be of significance in renal deterioration, especially in combination with reflux (Schmidt *et al.*, 1973;

Bergman, 1978; Pernet, 1985). Other authors have found no correlation between bacterial growth and renal deterioration (Kafetsioulis, 1968; Philip, 1980).

In patients with continent caecal reservoirs, Månsson (1984) found symptomatic pyelonephritis only in combination with outflow obstruction.

Skinner (1987) reported that of 250 patients with urinary diversion via a continent ileal reservoir, pyelonephritis was observed in 6, 4 of whom had malfunction of the anti-reflux nipple valve. Similar findings concerning the significance of bacteriuria were revealed in a recent study in this unit (Åkerlund *et al.*, in preparation). The constant or intermittent bacteriuria in patients with urinary diversion via a continent ileal reservoir cannot be judged harmful to the upper urinary tract, provided that the anti-reflux valve is competent and that there is no outflow obstruction.

Gastrointestinal mucus is defined as the viscous, slippery gel that covers and protects the surface of the entire gastrointestinal tract. It contains a complex mixture of glycoproteins (mucins), water, various serum and cellular macromolecules, electrolytes, micro-organisms and sloughed cells (Neutra and Forstner, 1987). Even if the composition of urine centrifugate in the present study differs from that of gastrointestinal mucus, it is reasonable to believe that the stable weight of the urine centrifugate accurately reflects an unchanged production of mucus of the reservoir mucosa. This finding confirms the observation that mucus production in our patients did not decrease with time and is in agreement with the report of Murray *et al.* (1987), who also found no decrease in mucus production in patients with caecocystoplasty, ileocystoplasty or ileal conduit diversion. Moreover, the admixture of mucus to urine does not impede the evacuation procedure in our patients, who use a Medena tube (24 F) for catheterisation.

This study has shown that the daily management of the continent ileal urostomy involves little inconvenience to patients when compared with normal voiding habits. However, the presence of a cutaneous stoma and the necessity for catheterisation should not be ignored. Urinary output is significantly increased but is compensated for by a larger fluid intake. The total output of electrolytes and osmoles during 24 h is similar to that of normal individuals, indicating that transport across the ileal mucosa does not interfere with the electrolyte and fluid balance. The urinary reservoir usually contains bacteria but this bacteriuria seems to be harmless provided that the anti-reflux valve prevents ascending infection; treatment with medicaments is therefore unnecessary. Mucus production did not diminish with time.

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Videoprostatectomy. Guidelines for Choosing an Effective Microvideo Operating System

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Summary—Videoprostatectomy is gaining increasing acceptance by urologists. Guidelines are suggested to assist in the selection of a suitable video operating system and to optimise both the quality of the video image and safety of operation.

Videoprostatectomy is transurethral prostatectomy performed using a microvideo camera attached to the lens of the resectoscope, thereby avoiding the need to work whilst peering down a telescope (O'Boyle *et al.*, 1984, unpublished observations). The technique has been shown to be safe and efficient and is gaining increasing acceptance by urologists (Appleton *et al.*, 1984, unpublished observations; Widran, 1987; Yachia, 1987).

Traditional endoscopic prostatectomy imposes significant physical demands on the operator and the bizarre postures adopted by the surgeon in his quest for the complete prostatectomy are remarkable. The standard operating position, with hands above shoulder level and head buried deep in the perineum of the patient, is both physically tiring and aesthetically unacceptable. The proximity of the surgeon's face to the operation field instantly contaminates both the equipment and the sterile drapes, which might reasonably be regarded as protection for the surgeon rather than the patient. Finally, intense boredom is generated by a lengthy endoscopic session in other members of the operating team and theatre staff.

With these considerations in mind, it seemed sensible to exploit new video microtechnology. Having gained 6 years' experience with video-endourology, we wish to emphasise the advantages of the technique and to try to resolve some of the difficulties encountered by urologists in the selection of an effective video operating system.

Fundamental requirements for effective prostatectomy are a good optical telescope, an adequate light source, a microchip miniature video camera, a suitable video monitor and a compatible diathermy system. Last, but by no means least, the enthusiasm of the surgeon is essential, since it is necessary to devote much time to a personal appraisal of the various microvideo systems available and to gaining experience with the new technique.

Telescope

A good optical telescope in prime condition is fundamental and whilst the equipment produced by the major manufacturers is of outstanding quality, it can readily be damaged by vigorous and frequent handling. The most common fault, resulting in an unsatisfactory video operating system, is a telescope in poor condition, producing misting, distortion or lack of resolution in the video image.

Misting is caused by condensation at the interface between the camera and the telescope lens and is due to temperature differences between the perfusing fluid and the equipment. The perfusing fluid should be maintained close to body temperature in order to prevent the risk of hypothermia during a lengthy resection. Other routine precautions against misting include immersion of the telescope in alcohol after disinfection and the use of proprietary anti-misting detergent solutions.

Light sources

A wide selection of light sources (price range £2000–

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£10,000) is available. Many of the less expensive items will produce a perfectly reliable video image. Intensity and colour will vary with different metal halide or xenon systems, and this is largely a matter of personal preference.

It should be noted that not all light sources produce cold light. There is a risk of an anaesthetised patient receiving a thermal burn from careless handling of a powerful hot light. There also remains the unresolved question of whether the light intensity may affect the retina of the surgeon if switching suddenly from the video camera to direct vision. The light intensity should, therefore, be slowly reduced should the surgeon wish to revert to direct vision. Careful reduction of light intensity also minimises the risk of damage to the expensive beam production unit. However, this is rarely necessary when using modern anaesthetic techniques and an efficient microvideo system.

Microvideo camera

In the early 1980s only one satisfactory microchip camera fulfilled the requirements for size, weight, robustness, reliability and disinfection. This was produced by Syn-optic and remains the camera of choice in Taunton. It has been extremely reliable during 6 years' continous use and has not required servicing during that time.

Increasing interest in video technique over the last 2 years has resulted in a plethora of microvideo cameras. Each system is different and prices range from £3000 to £13,000. Individual preference and financial circumstances will dictate the final choice. Some surgeons prefer to operate in pastel shades whilst others favour a more precise image and harder colours. The wide range of camera accessories includes an in-line beam splitter which enables the surgeon to make a direct visual inspection without detaching the camera. This facility is helpful only in the early learning stages.

Video monitor

The microvideo camera can be attached to any television monitor which is compatible with the signal. The PAL format is standard throughout Europe, but if travelling abroad it is wise to check well in advance that a suitable monitor is available. The quality of the image will depend both on the compatibility of the system and the size of the screen. Some of the more sophisticated monitors will reject impurities in the signal, produced particularly by the earlier video cameras, and the result will be a black and white picture or loss of definition. Current prices range from £400–£1100. We prefer a 7" screen which can be positioned over the patient's abdomen on a Mayo stand thus allowing a more comfortable operating position, known as the "armchair prostatectomy". The high magnification of the image makes tissue definition, in particular capsular fibres, quite outstanding.

Several monitors may be introduced to allow viewing by the anaesthetist, other theatre staff and students, or inside the operating theatre by means of a suitable cable link. If several monitors are introduced, professional advice should be sought, since it may be necessary to boost the signal in order to produce a satisfactory image.

Compatible diathermy system

Radiofrequency (RF) interference from incompatible diathermy is one of the most irritating difficulties encountered when using a video operating system. Interference may range from total obliteration of the image whenever the diathermy pedal is pressed, to a "seeing stars" effect superimposed on the prostate image.

Every diathermy system produces its own characteristic pattern of RF interference, ranging from horizontal and vertical bars to a bewildering array of stars, dots and lightning flashes. Even the same model can produce remarkable individual variations. The various cutting and coagulation current frequencies can also produce different patterns. On some occasions the RF pattern may be abolished by using blend. At other times, blend actually accentuates the interference.

It is important to realise that diathermy interference can usually be eliminated and that this should be conditional on the choice and purchase of any video operating system.

Video cassette recorder (VCR)

A VCR is an extremely useful optional extra. The choice is enormous (VHS, compact 8 mm, commercial U-matic and Hi-band) and will depend on the individual requirement. Our choice of a VHS system was determined largely by economy and flexibility, based on the cost of tapes and editing facilities. The system is used mainly for playback for teaching purposes, for keeping records of individual patients and for unusual findings. If the objective is to produce high quality videos for presentation at international meetings, U-matic may be a wise choice, but this is more expensive and not all conference venues can provide suitable playback equipment.

Videoprostatectomy is becoming established as a safe and effective operating technique in transurethral surgery. The advantages include greater comfort for the operator combined with less stressful operating conditions. General participation by all theatre staff, including anaesthetists, trainees and nursing staff, makes endoscopic sessions significantly more rewarding for everyone involved.

A wide range of equipment is now available but the final choice must be determined by personal preference and by cost. It is vitally important for surgeons to select systems and accessories which satisfy their personal requirements and to ensure that the system purchased is compatible with existing equipment and adequate for modern operating purposes. Considerable time must be spent on the proper evaluation of the various systems in order to avoid disappointment when the system is finally installed.

We consider the following to be desirable features when evaluating the microchip camera.

Small size and light weight. New models will continue to become smaller and lighter. This may be at the expense of more important features and size alone should not dictate the final choice.

Fully immersible camera, camera cable and plug. Since the camera head, cable and plug must be handled by a scrubbed nurse, a fully immersible system is desirable. Some cameras require that the plug is not immersed, some have a plug cap which may not provide an adequate seal, and some plugs are a moulded assembly which may be immersed with the camera. The latter is most desirable since it is designed to be compatible with Cidex rather than requiring protection from it. This also means that the whole assembly can be placed on a trolley before plugging in. Plugs not designed to be exposed to a moist environment will prove unreliable under normal operating conditions. All plug assemblies are expensive and time-consuming to replace.

Replaceable camera cable. Since the completely sealed camera head is designed to be as small as possible, it is easier to design the cable with a bonded gland to the camera. However, this means that if the camera cable or plug is damaged, the whole unit must be returned to the manufacturer. Since the camera cable is the most vulnerable part of the entire system, this is very inconvenient. Some more sophisticated cameras have a plug and socket integrated to the camera, allowing the camera cable to be quickly changed without risk of damaging the seal.

Flexible camera cable. As the range of equipment being attached to endoscopes increases, a light flexible camera cable becomes an advantage. Some cameras are still supplied with very rigid cables.

'C'—mount for optical adaptors. If the camera head accepts optics with a 'C'-mount thread, a wide range of optical couplers to the endoscope can be used either now or in the future. This will enable the use of direct couplers, when viewing from the monitor, or beamsplitter couplers for simultaneous direct view. In addition, various focal length couplers will enable the image size to be corrected when using small diameter endoscopes. This flexibility will allow equipment to be shared and offers compatibility with endoscopes of the future.

High quality video output. This is difficult to assess and cannot be judged from a monitor (which has automated correction circuitry). Some surgical cameras are derived from the most inexpensive home video cameras and although image quality may appear satisfactory on a small monitor, the lack of definition will be apparent on video tape (especially if edited) and on large screen projection. Some of the latest devices designed to produce colour prints from video cameras will not produce satisfactory results with an inferior signal.

Reliability. This is difficult to assess accurately, but close liason with colleagues will give a good indication.

Video recorder/printer button. Several models provide a button on the camera itself which can be used to trigger a video recorder or printer. This reduces the need for continued verbal instructions to theatre staff.

Simplicity of operation. The camera control unit should be as simple as possible. In practice, a colour bar pattern output has been found useful when monitoring the system. Controls need only include power, colour (manual is preferable to auto white), gain (or video level) and colour bar.

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Androgen and Oestrogen Receptor Status in Benign and Neoplastic Prostate Disease

Study of Prevalence and Influence on Time to Progression and Survival in Prostate Cancer Treated by Hormone Manipulation

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Summary—TUR chips from 89 men were analysed prospectively for androgen and oestrogen nuclear and cytoplasmic receptors (ANR, ACR, ONR, OCR). Patients were selected on the basis of suspicion of neoplastic change on clinical feel of the prostate. A control group of benign cases was also collected prospectively. Histological examination showed that 46 patients had prostatic carcinoma and 43 had benign prostatic hyperplasia. No difference was found between the 2 groups in terms of prevalence of any of the receptors or in levels of receptor in those who were positive. The patients with neoplastic changes were followed up for a median of 53 months (range 47–64). No significant effect on duration of survival was noted with any of the receptor variables but there was a beneficial association between cytoplasmic oestrogen receptor positivity and progression-free interval. Patients with T category 3 or 4 had a significantly higher chance of being ANR positive than those of lower T category and this may reflect sampling error. There appears to be some evidence to suggest that cytosol oestrogen receptor positivity has a prognostic role in prostate cancer, in terms of time to progression on hormone therapy. Receptor status did not influence survival.

It is well established that the human prostate is androgen-dependent (Cabot, 1896; Huggins and Hodges, 1941). Endocrine therapy for advanced carcinoma of the prostate is the most successful form of treatment and controls symptoms in over 70% of cases (Robinson *et al.*, 1974). Responses average 18 months in duration (Walsh, 1975), although the response to hormone treatment is variable; 10 to 40% of patients will not respond (Altwein, 1982) and there is minimal survival benefit between any of the forms of hormone therapy available (Byar, 1973).

The measurement of oestrogen and progesterone receptors provides valuable guidance for treatment and prognosis in breast cancer (Jensen, 1975). Human prostate also has both cytoplasmic and nuclear androgen and oestrogen receptors and these can now be measured reliably (Bashirelahi and Young, 1976; Bonne and Raynaud, 1976). It has been suggested that the measurement of androgen cytosol receptors is of value in predicting response to endocrine therapy (Ekman *et al.*, 1979). More recently, nuclear androgen receptor status has been shown to be at least a partial indicator of sensitivity to hormone manipulation (Ghanadian *et al.*, 1981; Trachtenberg and Walsh, 1982; Brendler *et al.*, 1984; Gonor *et al.*, 1984).

The aim of this study was to test the hypothesis that receptor status of patients with prostatic carcinoma was associated with duration of response and survival on hormone therapy. The prevalence of receptor positivity in 43 cases of benign prostatic hyperplasia is also reported and levels of receptor were compared in the benign and neoplastic groups.

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Patients and Methods

Patients undergoing transurethral resection of the prostate (TURP) were mainly selected on the basis of a gland that felt suspicious on bimanual palpation under anaesthesia. A control group of benign cases was collected at the same time. Thus 89 men (age range 49–87 years, median 71) had receptor analysis performed on 4 to 5 randomly chosen chips of prostate between September 1981 and February 1983. Specimens were stored in liquid nitrogen prior to analysis and all assay procedures were carried out at 0 to 4°C. Both cytosol and nuclear (salt extractable) extracts were assayed for androgen receptor by incubation for 18 h at 4°C with labelled synthetic androgen R1881, with the addition of triamcinolone acetonide to eliminate possible binding of cytoplasmic progesterone binding protein (Zava *et al.*, 1979). Unbound R1881 was removed with dextran charcoal and the residual bound radioactivity measured by a scintillation counter. Results were expressed as fmol/mg protein. A similar technique was used for the oestrogen assay except that the ligand was ^{3}H oestradiol.

All histological grading was performed by a single pathologist using the Gleason classification (Gleason, 1966). The scores were summed for purposes of analysis. The pathologist also estimated what the level of receptor would be if each tumour was 100% malignant, by assessment of several sections of histological material from each patient. This "corrected androgen level" was used as a discrete variable in the analysis (ACOR).

In patients with carcinoma the following assessments were made at baseline and every 3 months: T category, serum creatinine and acid and alkaline phosphatases. M status by means of isotope bone scan ±X-ray was assessed 6-monthly or as clinically indicated. Scoring of pain, urinary flow and performance status was also carried out at each visit. Six patients were lost to follow-up and have been excluded from the analysis. No follow-up was carried out on benign cases.

Systemic treatment was given only to symptomatic patients, either with bone or perineal pain or recurrent bladder outlet obstruction. The latter was treated by transurethral resection and systemic therapy.

Disease progression was defined as an increase in bone or perineal pain warranting an increase in analgesia requirement, an increase in urinary outflow symptoms necessitating further transurethral surgery, or an increase in the number or extent of bone secondaries shown on isotope bone scan.

Cause of death was recorded from hospital records and Cancer Registry data. All life table and chi-square analyses were carried out using the Bio-Medical Data Package (University of California) on a systime minicomputer. The Kruskal-Wallis test was applied to compare the levels of receptor in benign and malignant cases.

Results

Benign prostatic hyperplasia was diagnosed in 43 patients and prostatic carcinoma in 46. Age ranges and the frequency of the 4 types of receptor measured were similar in both groups (Table 1); 28 cancer patients (70%) were positive for androgen cytoplasmic receptor (ACR) compared with 23 benign cases (53%), but this difference was not statistically significant. Absolute values of androgen nuclear and cytoplasmic receptor in the positive patients showed no difference between the benign and malignant groups (Table 2). However, oestrogen receptor levels in both nuclear and cytoplasmic fractions in neoplastic prostates were significantly higher than those in the benign hyperplasia group ($P = 0.024$ and $P < 0.001$ respectively). In the neoplastic patients, those with T category 3 or 4 were significantly more positive for ANR than were those with T0–2 ($\chi^2 = 4.1$, DF = 1, $P = 0.04$), but no significant relationship existed between either

Table 1 Hormone Receptor Prevalence in 89 TUR Cases

	Benign prostates (age range 52–81 years; median 69) N = 49	
	Present (%)	*Absent (%)*
Androgen		
Nuclear	25 (58)	18 (42)
Cytoplasmic	23 (53)	20 (47)
Oestrogen		
Nuclear	24 (56)	19 (44)
Cytoplasmic	22 (51)	21 (49)
	Neoplastic prostates (age range 49–87 years, median 72) N = 40	
	Present (%)	*Absent (%)*
Androgen		
Nuclear	24 (60)	16 (40)
Cytoplasmic	28 (70)	12 (30)
Oestrogen		
Nuclear	22 (55)	18 (45)
Cytoplasmic	17 (43)	23 (57)

Table 2 Receptor Content (fmol/mg protein) in Neoplastic (N) and BPH (B) Cases

	ANR (N)	*ANR (B)*	*ACR (N)*	*ACR (B)*	*ONR (N)*	*ONR (B)*	*OCR (N)*	*OCR (B)*
	85	30	25	14	46	6	33	6
	72	36	32	76	25	25	19	15
	126	30	76	25	113	33	25	50
	31	26	49	50	88	16	12	2
	52	29	12	53	58	4	43	10
	54	88	15	4	109	11	101	13
	41	87	66	5	8	8	19	9
	34	31	20	2	8	37	20	2
	26	8	8	36	3	8	12	5
	34	24	48	36	8	10	5	1
	186	38	91	94	40	7	15	18
	112	20	28	15	24	20	36	4
	77	205	25	48	15	41	45	5
	64	19	6	197	14	31	20	7
	6	36	13	9	34	5	31	15
	91	3	14	3	35	7	25	2
	13	2	116	9	20	19	6	4
	122	37	20	3	48	14		1
	65	11	50	14	20	9	••	6
	74	57	42	68	25	32		4
	26	44	189	43	48	12		25
	40	65	9	123	3	35		14
	16	19	41	243		14		
	11	40	5			4		
		175	14					
			143					
			24					
			30					
Mean	60 75	46.40	43.25	50.87	36.00	17 00	27.47	9.91
SD	42.74	47.64	43.42	61.23	31.05	11.57	21.61	10.70
SEM	8 73	9.53	8.21	12.77	6.62	2.36	5 24	2 28
N	24	25	28	23	22	24	17	22
Kruskal-Wallis test; levels of significance								
	$P=0.097$		$P=0.857$		$P=0.024$		$P<0\ 001$	

ANR or OCR and summed Gleason score, T category or M status.

Treatment was given to 32 patients. This consisted of stilboestrol 1 mg 3 times a day in 25 patients. Patients with pre-existing or concurrent cardiovascular complications were treated by orchiectomy (4 cases). Those who refused orchiectomy were treated with cyproterone acetate 100 mg *tds* (3 patients); 16 patients (50%) were initially asymptomatic and were treated after a median of 7 months (range 3–51) from the date of TURP; 8 patients have remained asymptomatic and have required no treatment over the follow-up period, but 4 of these were in a good prognostic group in terms of T category and M status T0–2 M0) (Table 3).

Signs of progressive disease on follow-up were seen in 34 patients. Of the remaining 6, 4 have had no treatment and 2 are stable on treatment; 29 patients died during follow-up. All but 2 died at home and post mortem reports were available on these 2 only. In 22 patients the primary cause of death was prostate cancer; 2 died of stroke and 3 of congestive cardiac failure. One of these was not on any treatment for his carcinoma. Two patients died of other malignant disease. All causes of death were used in the analysis, since there was no significant difference in the life tables when all deaths were compared with prostate cancer deaths only.

All of the receptor variables, as well as baseline clinical and biochemical assessments, were grouped into positive or negative, normal or high, and patients were analysed by survival and time to progression using the logrank technique (Table 4). The first difference of note was in the survival of the untreated versus the treated patients. As mentioned above, 4 of 8 patients who were not treated (other than TURP) had no bone disease and T0–2 tumours. The longevity of this group was put down to these factors and when the groups were

Table 3 Details of 40 Patients with Prostatic Carcinoma According to T Status

No	*Grade delay in treatment (sum)*	*ANC*	*ACR*	*ACOR*	*ONR*	*OCR*	*T status*	*M status*	*Treatment*	*Delay in treatment (months)*
		(fmol/mg protein)								
3	3	0	32	1300	0	19	0	0	N	–
26	5	0	0	0	8	19	0	0	N	–
6	6	91	0	1037	0	0	1	1	Y	6
10	2	0	25	600	46	33	1	0	N	–
30	8	0	42	67	48	31	1	1	N	–
4	5	0	0	0	0	0	2	0	Y	9
8	6	0	116	250	0	0	2	1	Y	0
11	5	31	0	37	0	0	2	0	Y	14
12	5	52	12	218	58	43	2	0	Y	51
20	6	77	25	188	0	0	2	0	Y	–
21	5	0	15	10	0	0	2	0	N	–
40	8	0	0	0	20	0	2	0	Y	6
2	9	0	9	0	48	25	3	1	Y	0
5	4	126	0	400	88	0	3	1	Y	0
9	–*	0	20	–	35	45	3	1	Y	0
17	–*	112	28	–	0	0	3	0	Y	6
23	5	54	0	177	109	101	3	1	N	–
28	6	13	0	0	34	36	3	0	N	–
29	9	0	0	0	20	20	3	1	Y	0
32	5	41	66	324	8	0	3	1	Y	0
33	6	64	13	5800	0	5	3	0	Y	4
34	–*	72	49	–	0	12	3	0	Y	17
35	9	26	14	90	2.5	0	3	1	Y	3
36	6	56	0	0	14	15	3	1	Y	0
37	5	34	20	617	3	20	3	0	Y	9
39	5	26	8	57	8	12	3	1	Y	0
1	8	0	0	0	0	0	4	1	Y	3
7	9	40	243	407	0	0	4	1	Y	0
13	10	16	24	54	0	0	4	1	Y	8
14	10	11	30	49	0	0	4	0	Y	0
15	6	34	48	261	40	0	4	1	Y	0
16	6	186	91	312	0	0	4	1	Y	0
18	9	0	41	65	0	0	4	1	Y	0
19	8	122	50	267	0	0	4	0	Y	0
22	–*	65	189	–	25	0	4	1	Y	4
24	9	74	5	181	0	6	4	0	Y	0
25	3	0	0	0	25	0	4	1	Y	6
27	6	0	6	0	24	0	4	1	Y	0
31	3	85	76	2860	113	25	4	0	N	–
38	6	0	14	0	15	0	4	1	Y	8

* Missing Trucut biopsy cases, hence no ACOR either

split into T0–2 M0 and T3–4 M1, a similar picture emerged (Table 4). As a result, all of the other variables were examined with and without these 8 cases. The presence of ANR conferred no benefit on prognosis on analysis of all treated cases. The only significant result was the association between OCR positivity and longer progression-free interval ($P = 0.002$, treated patients only) (Table 4) (Fig.).

Discussion

Most prostate cancers are hormone sensitive, but there remains a significant number that will not respond to hormone manipulation. The concept that the androgen receptor status of prostatic tumour should provide a guide to the response of the tumour to hormone manipulation has been an attractive one, but clinical and laboratory corroboration has met with limited success. Androgen nuclear receptor (measured as fmol/mg DNA) is the only receptor measure showing any significant correlation with duration of response and survival (Trachtenberg and Walsh, 1982), with a cut-off of 110 fmol/mg DNA between good and poor prognosis. Ghanadian *et al.* (1981) suggested 500 fmol/mg DNA as a cut-off between good and poor

Table 4 Results of Logrank Analyses. Survival by Groups (all causes of death)

Variable	*Cases used*	*Groups and No.*	*Statistic (DF=1)*	*P*	*Group Favoured*
ANR	40	24+/16–	5.492	0.019	–ve
ANR	32	21+/11–	1.883	0.170	
ACOR	28	19+/9–	0.261	0.609	
ACR	32	23+/9–	0.043	0.835	
ONR	32	16+/16–	0.592	0.442	
OCR	32	10+/22–	0.817	0.366	
Tcat	40	12(0–2)/28(3–4)	2.861	0.091	0–2
Grade	36	14(1–5)/22(6–10)	4.096	0.043	1–5
M status	40	18(0)/22(1)	4.213	0.040	
					0
ALKP	39	27 norm/12abn	5.078	0.024	norm
AP	39	25 norm/14 abn	0.567	0.451	
Treatment	40	8 none/32 some	4.527	0.033	none
T0–2 M0/T3–4/M1	40	9/31	5.892	0.015	T0–2, M0

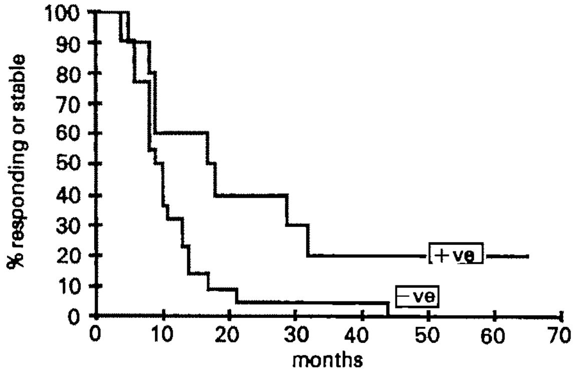
Time to progression by groups

Variable	*Cases used*	*Groups and No*	*Statistic (DF=1)*	*P*	Group favoured
ANR	32	21+/11–	0.005	0.942	
ACOR	28	19+/9–	0.360	0.548	
ACR	32	23+/9–	3.083	0.079	+ve
ONR	32	16+/16–	0.108	0.742	
OCR	32	10+/22–	9.873	0.002	+ve
T cat	32	7(0–2)/25(3–4)	0.029	0.865	
Grade	28	8(1–5)/20(6–10)	0.075	0.784	
M status	32	12(0)/20(1)	0.453	0.501	
ALKP	31	19 norm/12 abn	0.867	0.352	
AP	31	18 norm/13 abn	0.843	0.359	
Treatment	40	8 none/32 some	5.716	0.017	none
T0–2, M0/T3–4/M1	40	9/31	2.331	0.127	

Cases used were all cases except where values were missing (4 Grade, 4 ACOR, 1 ALKP, 1 AP) or where the analysis excluded the 8 untreated cases.

response to endocrine therapy, but numbers are relatively few in both series. On the other hand, most workers have found that oestrogen receptor levels are not very different in benign and neoplastic prostatic disease (Donnelly *et al.*, 1983; Ekmann *et al.*, 1983). However, this study has shown significantly higher nuclear and cytoplasmic high affinity oestrogen receptor levels in neoplastic compared with benign hyperplasia (Table 2), but with equivalent rates of positivity for receptor as the above series. This finding, along with the relationship of oestrogen cytoplasmic receptor positivity to duration of response, supports the work of Jasper *et al.* (1987), who found that both oestrogen and androgen positivity was linked to increased duration of response. Sidh *et al.* (1979) also reported a relationship between oestrogen receptor content and responsiveness to endocrine therapy. Monoclonal antibodies raised against breast and endometrial oestrogen receptor do not react with prostate, suggesting an antigenic difference between the oestrogen receptors in prostate (Pertschuk *et al.*, 1985). ^{3}H-oestradiol has been shown to bind to epithelioid prostate cancer cells using autoradiography (Beckman *et al.*, 1985). There is some evidence that the stromal tissue of benign hyperplasia contains an abundance of oestrogen (oestradiol) and this has lead to the suggestion of a role for oestrogen in the aetiology of benign hyperplasia (Kozak *et al.*, 1982).

This study has failed to demonstrate a relationship between tumour response to endocrine manipulation and androgen receptor status, but does demonstrate a significant beneficial effect of oestrogen cytoplasmic receptor positivity on time to progression. None of the receptor variables had any effect on survival (Table 4). M status and summed Gleason score (1–5, 6–10) were significant



No at risk							
Oestrogen cyt. rec. −ve	22	10	2	1	1		
Oestrogen cyt. rec. +ve	10	8	5	4	3	3	1

Fig. Oestrogen cytoplasmic receptor status and time to progression (8 untreated cases were excluded). Mantel-Cox statistic = 9.87, DF = 1, $P = 0.0017$ Median time to progression was 9 months for −ve group and 18 months for +ve group.

prognostic variables for survival in this series but T category was not, though there was a trend favouring the lower group ($P = 0.091$) (Table 4).

Sampling is a major source of error in any such biological study. In this study only a small proportion of the resected specimen was selected for analysis; the remainder was needed for histological grading. In the analysis, it was discovered that patients of low T category had a significantly lower detection rate for ANR than those of higher T category; the former patients featured strongly in the untreated group, causing a significant bias; they were not included in the main analysis (Table 4). No such bias was found in the OCR positive cases on comparing this variable with summed Gleason score, T category or M status.

The assay method used avoids the problems of sex hormone binding globulin contamination and metabolisation of the probe during incubation. Receptor may be destroyed by electrocautery, but we analysed tissue taken by transrectal biopsy as well as resection in 4 patients and found similar levels of receptor in each. Most studies, including this one, show that receptor levels vary widely (Table 3) and in spite of the problems with estimation mentioned above, the variability of tumour response may be a reflection of both of these. Mobbs and Connolly (1987) suggested also that nuclear receptor results should be reported in fmol/mg DNA to avoid discrepancies in cellularity when comparing benign and malignant tissue; this was not part of this study protocol.

The proportion of malignant tissue varies between tumours and between parts of the same tumour. In the cases in this series the range was 1 to 54%. In an attempt to correct for these factors the pathologist (P.J.S.D.) estimated what the level of receptor would be if each tumour was 100% malignant, by assessment of several sections of histological material from each patient. Positivity for this "corrected androgen level" (ACOR) also failed to correlate with either time to progression or survival. This study would have to be repeated, using larger numbers, to be able to confirm the method as one of clinical value, but we do not think this is justified in view of the recent advances in histochemical techniques, using monoclonal antibodies against various markers of prostatic tissue, which are currently being evaluated (Wang *et al.*, 1979; Pertschuk *et al.*, 1985). These do not suffer the same technical difficulty with assay which are present with receptor studies, although they do have problems of their own (Connolly and Mobbs, 1984). In conclusion, although the presence of cytosol oestrogen receptor may influence tumour response to oestrogen therapy, the mechanism remains unclear.

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Anti-hormone Treatment for Prostate Cancer Relapsing after Treatment with Flutamide and Castration

Addition of Aminoglutethimide and Low Dose Hydrocortisone to Combination Therapy

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Summary—The effect of further adrenal androgen blockade with aminoglutethimide (AG) plus low dose hydrocortisone (HC) was studied in 119 patients with clinical stage D2 prostate cancer who previously progressed after standard hormone therapy and were under progression while receiving the combination therapy with Flutamide and castration. Using the objective criteria of the US NPCP, 1 complete, 2 partial and 14 stable responses were obtained for a total response rate of 14.3%, while 102 patients continued to progress. The 50% probability of survival was 21.0 months for the responders and 9.2 months for the non-responders. The present data indicate that further androgen blockade with AG + low dose HC is well tolerated and can be of benefit to a significant proportion of patients in progression at a very late stage of the disease.

A major problem facing the treatment of advanced prostate cancer is the lack of response as well as interruption of response to first-line endocrine therapy. Since the observation of Huggins and Hodges (1941), first-line endocrine therapy has been the neutralisation of testicular androgens by orchiectomy or oestrogens (Mettlin *et al.*, 1982) and, more recently, by LHRH agonists (Labrie *et al.*, 1980, 1986). Following such neutralisation of testicular androgens, 20 to 40% of patients are left in progression with no response at the start of treatment, while relapse of the disease is generally seen within 6 to 24 months in all of those who initially respond (Resnick and Grayhack, 1975). At the time of relapse, the median life expectancy is only 6 months (Johnson *et al.*, 1977). Our approach for these patients showing disease progression following treatment by orchiectomy, oestrogens or LHRH agonists alone has been the addition of the antiandrogen Flutamide with an objective positive response rate of 34% (Labrie *et al.*, 1988).

An important advance in the first-line endocrine therapy of advanced prostate cancer has been combination therapy or the association of a pure antiandrogen to castration at the start of treatment. As shown by open (Labrie *et al.*, 1986, 1987a) and randomised (Labrie *et al.*, 1985; Ojasoo, 1987; Benson *et al.*, 1988) trials, the rate and duration of response as well as survival are improved by the additional blockade of androgens achieved by a pure antiandrogen. However, 5 to 10% of patients do not respond to combination therapy and relapse of the disease, although markedly delayed compared with standard monotherapy, occurs in 60% of patients within 2 years (Labrie *et al.*, 1987).

The next and most difficult question is which treatment should be used in those patients showing lack of response or relapse of the disease under combination therapy. The present study investigated the effect of adding the inhibitor of adrenal steroid biosynthesis, aminoglutethimide, plus a low replacement dose of hydrocortisone to combination therapy in stage D2 patients in relapse or not responding to the association of Flutamide and

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castration. All of these patients had previously failed to respond to standard endocrine therapy.

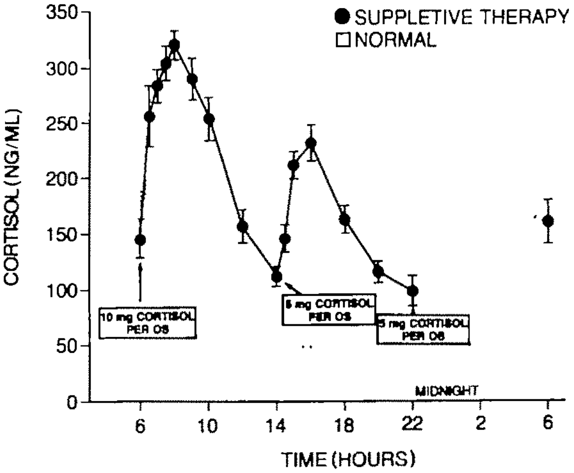

Fig. 1 Profile of serum cortisol concentration in 15 prostate cancer patients receiving the indicated doses of hydrocortisone acetate compared with control circadian rhythm in 20 untreated patients of similar age

Patients and Methods

All patients with biopsy-proven stage D2 prostatic carcinoma had disease progression following orchiectomy or treatment with diethylstilboestrol (DES) or an LHRH agonist alone. They were entered into the study after written informed consent. Flutamide 250 mg (orally every 8 h) was then given alone in castrated patients or in combination with the LHRH agonist [D-Trp^6, des-Gly-NH$_2$^{10}]LHRH ethylamide (LHRH-A) 500 μg s.c. daily for the first month, followed by 250 μg s.c. daily, to those previously treated with DES or another LHRH agonist. The oestrogen or other LHRH agonist was replaced by LHRH-A in all cases.

Patients who did not respond or who relapsed while receiving the combination therapy with Flutamide received aminoglutethimide and hydrocortisone. Aminoglutethimide 250 mg 3 times a day was given orally for the first 3 weeks followed by 250 mg 4 times a day, unless the patient complained of lethargy associated with the soporific side effects of the drug. If side effects such as lethargy, nausea, ataxia or dizziness became clinically significant, the dose of AG was temporarily reduced until the signs and/or symptoms disappeared or became acceptable. The dose was then re-established to 1000 mg/day in 4 divided doses. A low dose of hydrocortisone acetate was given as glucocorticoid replacement, namely 20 mg daily (10 mg at 0700 h, 5 mg at 1500 h and 5 mg at 2300 h). As shown in Figure 1, this schedule and dose of HC was used in an attempt to reproduce the physiological nyctohemeral cycle of cortisol secretion.

Complete clinical, urological, biochemical and radiological evaluation of the patients was performed before the start of treatment and during the study as described (Labrie *et al.*, 1985). The initial evaluation included medical history, physical examination, haematology, serum biochemistry, urine analysis, flowmetry, chest X-ray, bone scan, skeletal survey, ultrasonography of the prostate and abdomen and, when indicated, computed axial tomography (CAT), nuclear magnetic resonance imaging (NMI) and intravenous urography (IVU). The same tests were performed after 3 and 6 months of treatment and then every third or sixth month or more frequently, depending upon the evolution of the disease.

Classification of response was performed according to the objective criteria of the National Prostatic Cancer Project (NPCP) (Slack *et al.*, 1984). Bone scans were evaluated by an independent group of radiologists unaware of the treatment of the patients. All measurements of serum prostatic acid phosphatase (PAP) and prostatic specific antigen (PSA) as well as serum levels of testicular steroids, adrenal steroids and pituitary hormones were performed at the Laboratory of Molecular Endocrinology, Laval University Medical Center, Quebec City.

The first reported evaluation of positive objective response was after 3 months' treatment. Patients were considered as non-responders if there was no objective stabilisation or regression of their disease at that time, even though there had been subjective benefits. Performance status and pain were evaluated on a scale of 0 to 4 according to the ECOG criteria.

In 72 patients (57%), orchiectomy was the first treatment. In those previously treated with an LHRH agonist alone or DES, serum testosterone levels were all in the orchiectomised range; 34 patients (27%) had received at least 1 course of radiotherapy for metastatic disease but none had received chemotherapy. Among the 126 patients entered into the study, 7 were not evaluated: 5 stopped therapy on their own and 2 were lost to follow-up. Thus 119 patients with an age range of 48 to 83 years (mean 66) were evaluated for their objective response to the addition of aminoglutethimide and low dose hydrocortisone to combination therapy.

Among the patients included in the study, 94 (74.6%) complained of pain (58 had pain permitting normal activity, 29 had pain interfering with daily activity and/or sleep, 5 were constantly suffering from pain and 2 had intolerable pain requiring 100% of time in bed); 35 patients (27.7%) were ambulant but symptomatic, 17 (13.5%) were bedridden less than 50% of the time, 5 (3.9%) were bedridden more than 50% of the time and 2 (1.6%) were 100% bedridden. Loss of body weight and appetite was present in 50 patients (40%). Location of metastases prior to the addition of aminoglutethimide and hydrocortisone included bone metastases in all patients, lung involvement in 10 (7.9%), pelvic and distant lymph nodes in 10 (7.9%), liver in 4 (3.2%), central nervous system in 1 (0.8%) and bone marrow in 1 (0.8%); 79 patients (62.7%) had elevated levels of serum prostatic acid phosphatase (PAP).

Calculations

Radioimmunoassay data were analysed using a program based on model II of Rodbard and Lewald (1970). Statistical significance was measured according to the multiple-range test of Kramer (1956). The probability of continuing response and survival was calculated according to Kaplan and Meier (1958).

Results

As shown in Table 1 and Figure 2, the addition of AG+HC to combination therapy led to a 14% objective response rate in patients progressing under combination therapy with Flutamide; 1 patient (0.8%) had a complete response, 2 (1.7%) had a partial response, 14 (11.8%) had a stable response and 102 (85.8%) continued to progress. In the latter group, 2 patients showed simultaneous disappearance of old lesions and appearance of new ones, thus suggesting heterogeneity of the androgen sensitivity of the tumours. As illustrated in Figure 2, the 50% probability of survival was 21.0 months for responders (curve A) and 9.2 months for non-responders, the difference between the 2 curves being highly significant ($P=0.0056$, log rank test) (Knudsen and Strom, 1986).

The most frequent side effect was lethargy (12 patients) (Table 2). Nausea was seen in 5 patients and skin rash and fever occurred in 4 cases; 1 patient needed replacement therapy with Florinef for symptomatic low blood pressure.

Discussion

The present data show that an objective response can be obtained in a small but significant (14%) proportion of patients in progression under combination therapy (Flutamide and castration) by additional blockade of adrenal androgen secretion achieved by AG+HC and that the therapy is well tolerated. We found that the addition of Flutamide to patients in relapse after standard endocrine therapy produced an objective response in 34.5% of 209 patients (Labrie *et al.*, 1988). The present data indicate that an additional 14% can benefit from further adrenal androgen blockade achieved by AG and low dose HC, making a total response rate of 48% in this difficult group of patients with disease progression after standard hormonal therapy.

Since most of the objective responses were in the stable category, it was important to establish that every patient was in real progression at the start of treatment with AG+HC and not already stable. In this regard it should be recalled that all of the patients were first seen in progression under standard endocrine therapy, namely blockade of testicular androgens by orchiectomy, DES or an LHRH agonist alone. Combination therapy with Flutamide was then given to all patients and a decision about further androgen blockade with AG−HC was not taken until 3 to 6 months later. In patients already castrated, Flutamide was given alone, and for those treated with DES, Flutamide was given in combination with the LHRH agonist

Table 1 Effect of Addition of Aminoglutethimide and Low Dose Hydrocortisone on the Objective Response Rate

Total evaluated	*Days of treatment mean (limits)*	*Objective response*			
		Complete	*Partial*	*Stable*	*Progression*
119	323 (85–943)	1 0.8%	2 1.7%	14 11.8%	102 85.7%
			14.3%*		

* 10.8% to 17.2% (95% confidence limits)

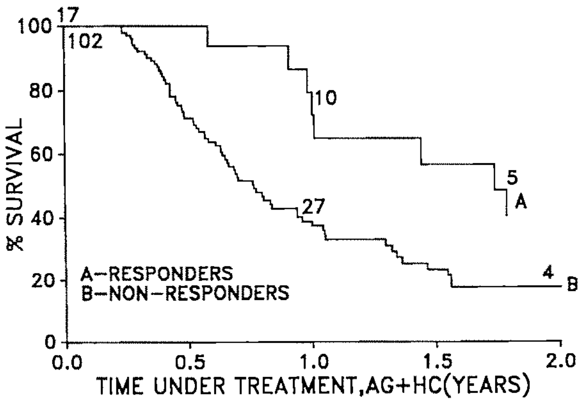

Fig. 2 Comparison of the probability of survival in stage D2 prostate cancer patients progressing under combination therapy and responsive to the addition of aminoglutethimide and hydrocortisone (AG + HC) (curve A) and the non-responders to the same treatment (curve B) The numbers on the curves indicate the number of patients assessed at each time interval. The two curves are statistically different ($P = 0.0056$, log route test (Knudsen and Strom, 1986)

[D-Trp^6, des-Gly-NH$_2$^{10}]LHRH ethylamide. In a study of 209 evaluable patients relapsing after standard monotherapy, 6.2, 9.6 and 18.7% achieved complete, partial and stable responses respectively, *i.e.* a total objective response rate of 34.5% to combination therapy (Labrie *et al.*, 1988). Coupled with the patients' excellent tolerance of this treatment, this response rate appears to make it the treatment of choice for prostate cancer patients in relapse after standard endocrine therapy.

Unfortunately, 65.5% of patients relapsing after monotherapy do not respond to the addition of the antiandrogen (Labrie *et al.*, 1988). Moreover, for the 34.5% of patients who initially respond, the mean duration of response is 24 months before a second progression occurs. The patients included in the present study are those who did not respond to the combination therapy as well as those who progressed after a variable period of response to such therapy. All 119 evaluated patients who received AG + HC were thus in clear progression under our observations for a minimal period of 3 months before the addition of AG + HC. It is thus unlikely that any of the stable responses observed correspond to patients already having stable disease before further blockade of adrenal androgens was achieved by AG + HC.

Table 2 Side Effects of Treatment with AG and HC

	No of patients	*%*
Adrenal insufficiency	0	0
Nausea	5	4.2
Rash	4	3.4
Lethargy	12	10.1
Fever	4	3.4
Dizziness	0	0
Thrombocytopenia	0	0
Leucopenia	0	0
Mineralocorticoid deficiency	1	0.8

The present approach, namely blockade of adrenal androgen secretion in patients relapsing under combination therapy, is based on the premise that tumours remain sensitive to the low concentration of androgens remaining free to activate the androgen receptor in castrated patients receiving Flutamide, and that aminoglutethimide associated with a low and near-physiological dose of hydrocortisone efficiently blocks adrenal androgen production.

Clinical data demonstrate that androgen-sensitive tumours are also present in patients who relapse after castration. These pertain to the findings that 34% of patients already castrated or treated with oestrogens or LHRH agonists alone show a positive objective response to the addition of Flutamide (Labrie *et al.*, 1988). That more than 95% of patients at the time of relapse have androgen-sensitive tumours is shown by the observation of a rapid exacerbation (within 3 days) of symptoms in 97% of relapsing patients treated with exogenous testosterone (Fowler and Whitmore, 1981).

Although AG has never been used in patients relapsing under combination therapy, the benefits of this drug have been observed in 30 to 60% of patients in progression after orchiectomy or treatment with DES (Robinson *et al.*, 1974; Drago *et al.*, 1984). Using the objective criteria of response of the NPCP, Drago *et al.* (1984) reported positive objective responses in 17 of 43 patients (40%) and Murray and Pitt (1985) observed 33% positive objective responses in 58 patients. In a study of 129 patients relapsing after castration, treatment with AG (1000 mg/day) and HC (40 mg/day) caused objective partial and stable remission in 9 and 33% of patients respectively, making a total objective response rate of 42% while 58% had disease progression (Crawford *et al.*, 1988).

A potentially important characteristic of the regimen AG-HC used in this study is the low dose of hydrocortisone used (20 mg/day), while all other reported studies used 40 or more mg HC/day as glucocorticoid replacement therapy. Crawford *et al.* (1988) used 100 mg HC during the first 2 weeks followed by 40 mg daily, Ponder *et al.* (1984) used cortisone acetate 50 mg/day and Drago *et al.* (1984)

and Murray and Pitt (1985) used 40 mg HC and 37.5 mg cortisone acetate daily respectively.

Although greater inhibition of adrenocortical activity could be achieved with higher doses of glucocorticoids, it is likely that such an approach has potential harmful effects on the immune system and on the evolution of cancer itself. It is of interest to recall the immunosuppressive properties of glucocorticoids. The secretion of interleukin-1 (IL-1) originating from monocytes as well as interleukin-2 and lymphotoxin from T-lymphocytes is suppressed by glucocorticoids (Mishell *et al.*, 1981). These steroids also block natural killer cell activity, possibly by inhibiting the production or release of specific cytotoxic factors. It has been shown that corticosteroids inhibit IL-1 production through an inhibition of the transcription of IL-1 encoding mRNA and thereby blocking cell-mediated immunity (Knudsen and Strom, 1986). With this knowledge of the role of the immune system in cancer, it seems logical to avoid the use of high doses of glucocorticoids, an approach which might have apparent short-term benefits but may well be responsible for an accelerated growth of the cancer.

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Optical Urethrotomy—Experience in Oman

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Summary—Over a 4-year period 170 men with urethral strictures were treated with optical urethrotomy; 80% required no further treatment during the 2-year follow-up; 2 patients with urethral fistulae associated with stricture were also treated successfully.

The Sultanate of Oman occupies the south-eastern corner of the Arabian Peninsula. With a land area of 271,949 square km and a population officially estimated for planning purposes at 1.5 million. Oman is the second largest country in Arabia.

Medical services are available at centres throughout the land but major surgical services are available only in the capital area—Muscat. A smaller surgical service is located in the south at Salalah.

Urological disorders are common and calculus disease forms the major part of the work. Urethral strictures, infective and traumatic, are also common and before 1981 were treated by intermittent urethral dilatation; impassable strictures, were overcome by suprapubic cystostomy and the retrograde passage of sounds with rail-roading of urethra. In 1982 one of the authors (J.C.S.) introduced the first optical urethrotome to the Sultanate. Earlier statistics for the number of strictures treated are unreliable, since many urethral dilatations were performed under local anaesthesia in peripheral centres and do not feature in the hospital records.

The Department of Urology was formed in April 1984, with a single full-time urologist (J.J.) being followed by a second (Q.B.) in 1986. Since then almost all strictures have been treated in the main hospital by optical internal urethrotomy and are the subject of this communication.

Patients and Methods

Patients are usually admitted on the morning of operation after out-patient investigation. Patients with acute retention who cannot be catheterised are treated with percutaneous suprapubic catheterisation and internal urethrotomy is performed on the next available operating list. Urethrograms are not usually performed. The procedure of internal urethrotomy is covered with Velosef and an indwelling catheter is left in place overnight. One litre of intravenous fluid is given post-operatively and the patient is discharged 1 day after operation. Antibiotic cover is provided for 5 days as many patients travel long distances in returning home.

Complications have been few, although some patients have developed extravasation of irrigating fluid into the periurethral space. There have been 2 cases of secondary haemorrhage and 1 of bacteraemic shock.

Even strictures with complications such as fistulas (Fig.) can be successfully treated transurethrally. We treated 2 such patients whose fistulae healed following internal urethrotomy.

The follow-up of patients is difficult as the population is distributed over a wide area. However, communication with the local medical officers is good and it is a reasonable assumption that any patient in serious difficulty would return to the Department of Urology.

Results

Table 1 shows the treatment record of 170 patients in the first 2 years and Table 2 shows the treatment record for the same group of patients in the subsequent 2 years.

Of the 145 patients in the first group who received

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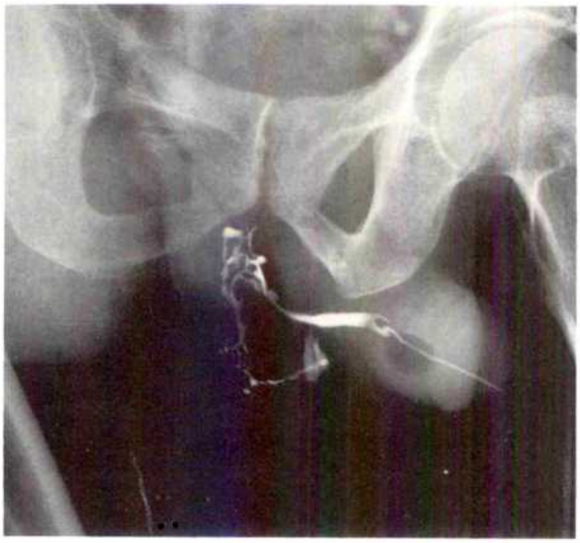

Fig. Urethrogram demonstrating urethral stricture with fistula.

Table 1 Patients Treated between April 1984 and March 1986

No. of patients (170)	145	17	3	4	0	1
No. of urethrotomies per patient	1	2	3	4	5	6

Table 2 Patients Treated between April 1986 and March 1988

No. of patients (18)	10	5	1	1	0	0	1
No. of urethrotomies per patient	1	2	3	4	5	6	7

a single urethrotomy, 9 required a further urethrotomy during the initial 2-year follow-up period. Of these 9 patients 7 received a total of 2 and 2 received 3 urethrotomies. Thus 136 patients (80%) were well during the 2-year follow-up period.

Only 18 of the 170 patients required further urethrotomy in the subsequent 2-year follow-up period. Of these, only 3 required urethrotomy more than twice. Our results confirm that optical urethrotomy is the treatment of choice for urethral stricture (Smith *et al.*, 1983).

The majority of strictures can be satisfactorily treated by a single internal urethrotomy, although a limited number (approximately 10%) require repeated treatment. Complicated strictures with fistulae can also be managed successfully by this method.

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Radical Retroperitoneal Node Dissection after Chemotherapy for Testicular Tumours

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Summary—A group of 29 patients underwent salvage node dissection for residual retroperitoneal masses following orchiectomy and combination chemotherapy for advanced testicular cancer between 1980 and 1988. The results confirm that surgery for residual retroperitoneal masses following combination chemotherapy is worthwhile and whenever possible the sympathetic chain should be preserved.

Although combination chemotherapy may be expected to shrink even large retroperitoneal metastases from testicular tumours, residual masses are not uncommon. When these occur, management is difficult. Should the mass comprise only fibronecrotic tissue or well differentiated teratoma, it may be unnecessary to remove it. Should it contain active cancer which has not responded to chemotherapy, operation may be dangerous and futile. Our more optimistic policy has been to attempt surgical excision of all potentially neoplastic tissue from the retroperitoneum (Donohue *et al.*, 1980; Ewing *et al.*, 1987; Hendry *et al.*, 1987). We have reviewed the outcome of salvage node dissections performed at the London Hospital over the last 8 years.

Patients and Methods

Between 1980 and 1988, 29 patients underwent salvage node dissection for residual retroperitoneal masses following orchiectomy, and combination chemotherapy for testicular cancer. Two patients had seminomas and 27 had non-seminomatous germ cell tumours. The age range was 17 to 53 years (mean 30). Mean follow-up was 33 months (range 6–93). Following surgery, the patients were seen at 3 to 6-monthly intervals for clinical examination, measurement of tumour markers (alpha fetoprotein and beta human chorionic gonadotrophin), chest X-ray and abdominal computed tomography (CT).

Most patients in the series were given 4 courses of bleomycin, etoposide and cisplatin (Oliver *et al.*, 1988). A few were initially treated at other centres: 3 patients had undergone previous retroperitoneal lumpectomy, 4 had received additional chemotherapy and 3 radiotherapy to the para-aortic and ipsilateral iliac lymph nodes. The decision to perform lymph node dissection was based upon a failure of the retroperitoneal masses to disappear entirely after completion of chemotherapy on CT scan.

Operative technique

Initially, a classical *en bloc* dissection was attempted (Dowd *et al.*, 1959; Donohue *et al.*, 1980) with ligation of the inferior mesenteric vessels, division of lumbar veins and arteries and full mobilisation of the aorta and vena cava from the coeliac axis down to the internal iliac arteries. The structures from the cava and aorta out to the ureter on each side were removed in 4 blocks, together with the tissue in front of and behind the great vessels (Blandy, 1986). More recently, attempts have been made, whenever possible, to protect the sympathetic chain on the side opposite to the tumour in the hope of preserving the ability to ejaculate (Donohue, 1984). In some cases this has meant identifying the sympathetic chain and rami com-

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Read at the 44th Annual Meeting of the British Association of Urological Surgeons in Buxton, June 1988

municantes and dissecting them away from the mass.

Results

Removal of the retroperitoneal mass was considered complete in all but 4 patients (14%). Resection of the bowel was necessary in 2 (7%) and minor breaches of the aorta required repair in 8 (27%). Tumours on the right side were often found to compress the vena cava and in 2 instances it was necessary to remove a length of cava along with the mass. No attempt was made to replace the missing vascular segment in these cases. There were no deaths within 6 months of the operation. One patient, who had been irradiated, developed a fistula from the sigmoid colon which required formal closure at a second operation. One of the patients whose vena cava had been resected suffered a pulmonary embolus despite prophylactic anticoagulation with subcutaneous calcium heparin.

Fibronecrotic tissue with no viable tumour was found in specimens from 13 (52%) of the 25 patients whose surgical removal was deemed complete. All of them remain well and free from recurrence 6 to 88 months following surgery (mean 40 months). The 9 patients (36%) whose mass consisted of mature teratoma have no evidence of disease 6 to 73 months following surgery, including 3 who had tumour beyond that apparent on the pre-operative CT scan. Active cancer was present in the 3 remaining patients (12%) who have so far declined further chemotherapy. They remain tumour-free 7, 10 and 66 months following surgery.

Four retroperitoneal masses could not be removed completely; 1 specimen consisted of fibronecrotic tissue without any tumour. The patient is alive and well 6 years later. In the second patient, who is disease-free at 7 years, the main part of the mass was made up of mature teratoma. The 2 remaining patients both had active cancer in the resected mass and it was impossible to remove all of the tumour, which extended through the psoas into the intervertebral foramina. Both of these patients developed further local recurrence, followed by widespread disease for which further chemotherapy has proved ineffective.

In 6 patients the serum tumour markers were elevated at the time of surgery; 2 were the patients referred to above whose tumour could not be removed completely, who had active cancer and now have widespread disease. In the remaining 4 patients no tumour could be found despite a careful pathological examination of the large mass of fibronecrotic tissue which comprised the specimen. In these patients the markers fell to normal after the operation and all remain disease-free with a mean follow-up following surgery of 24 months (range 6–49).

An attempt to preserve the sympathetic chain at least on one side was made in 9 patients, in the hope of retaining normal sexual function. As expected, all were able to achieve an erection and in 7 (78%) the ability to ejaculate was preserved. In the other 2 patients, dissection of the mass had to be continued down in front of the bifurcation of the aorta and the pre-sacral nerve had to be sacrificed.

Discussion

The removal of a large adherent mass of tissue from the posterior abdominal wall, aorta and vena cava presents certain technical difficulties. With care and attention to detail, morbidity and mortality are low. In our experience, pre-operative computed tomography does not accurately depict the limit of the disease: in 3 of 9 patients with mature teratoma in the resected specimen, tumour was detected in tissue away from the obvious mass. Three patients developed further retroperitoneal metastases following a lumpectomy performed elsewhere. In practice, therefore, total removal of all of the potentially involved tissue means a radical *en bloc* excision which may lead to an inability to ejaculate (Leiter and Brendler, 1967). We believe it is possible to modify the technique so as to preserve at least one sympathetic chain, the hypogastric plexus and presacral nerves.

Adequate pre-operative preparation makes bowel resection safer and easier. To mobilise the aorta and cava, all of the lumbar vessels must be ligated and divided—a task which requires time and patience. Even so, damage to the great vessels may occur because sharp dissection is often needed to remove the adherent mass. Resection of part of the vena cava can be performed with relative impunity. As a precautionary measure we control the aorta with tapes in every case and ensure that the expertise necessary to replace part of the aorta is available should the need arise.

These results justify the assertion that these masses should be removed, as surgery remains the only certain way to detect the presence of malignancy within the lump (Donohue *et al.*, 1982). Even in the presence of active cancer, the early outlook appears to be favourable following successful surgical removal, even though these patients have previously been judged to have a poor prognosis

(Tait *et al.*, 1984) and to require further chemotherapy (Vugrin *et al.*, 1981; Ellis and Sikora, 1987). Differentiated teratoma may not be a trustworthy entity and has the potential to become a more aggressive tumour (Einhorn *et al.*, 1981; Logothetis *et al.*, 1982; Ahlgren *et al.*, 1984). Even when the pathologist reports only fibronecrotic tissue, the possibility of tiny nests of undetected malignancy within a large mass cannot be discounted—a suspicion intensified by the finding of no tumour in 4 patients whose raised serum tumour markers fell to normal post-operatively. We can see no justification for withholding surgery simply because markers are elevated in patients with Stage II disease. As we have shown, they are still potentially curable by radical surgery.

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Case Reports

Emphysematous Cystitis

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Case Report

A 62-year-old woman was referred with pneumaturia. She had controlled diabetes mellitus. Blood glucose level was 200 mg/dl, haematocrit 33 vol/% and WBC count 7700/mm^3 with 42% neutrophils. Blood chemistry was otherwise within normal limits. Urine analysis showed 25 to 35 WBC/hpf and bacteriuria. A urine sample, cultured aerobically and anaerobically, yielded a significant growth of *Escherichia coli* only. An abdominal roentgenogram (KUB) showed an enlarged bladder with intraluminal gas (Fig. 1). The results of an IVU and post-voiding excretory cystography revealed residual urine (Fig. 2). The absence of vesicocolic and vesicovaginal fistulae was confirmed by contrast medium infiltration. She was treated with pipemidic acid orally for 7 days and her condition improved.

Comment

Emphysematous cystitis is a rare condition (Cohen *et al.*, 1984; Leduc *et al.*, 1985) and its pathogenesis is unclear. It is frequently found in patients with diabetes mellitus, an immunocompromised condition or residual urine. The condition results most commonly from infection with gas-forming aerobic bacteria such as *Escherichia coli, Proteus mirabilis, Klebsiella pneumoniae* and *Staphylococcus aureus*. Anaerobic bacteria and fungi are seldom detected (West, 1981; Singh and Lytle, 1983).

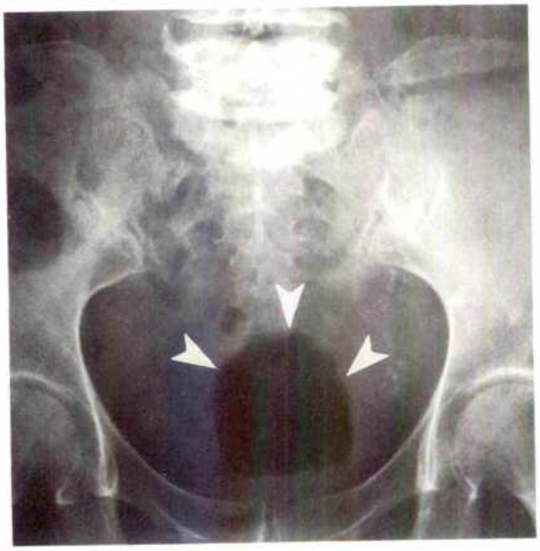

Fig. 1 Arrow heads show an enlarged bladder with intraluminal gas.

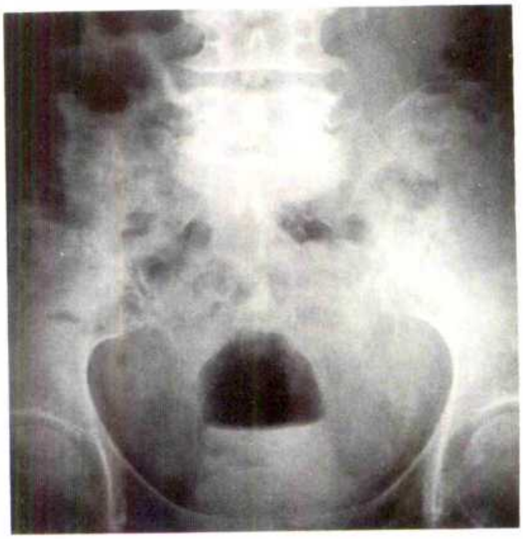

Fig. 2 Post-voiding excretory cystogram (standing) showing residual urine and intraluminal gas.

Treatment should be directed initially at establishing adequate bladder drainage and appropriate antibiotic therapy after early diagnosis.

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Ureteric Stents Caveat

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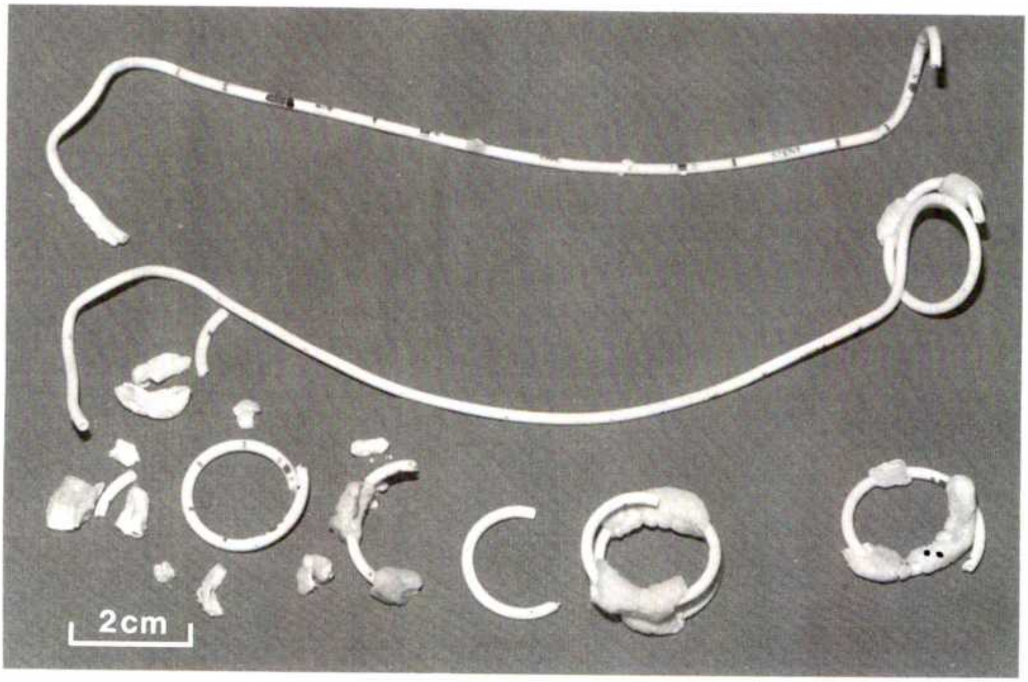
The use of silicon or siliconised tubes in the urinary tract has increased rapidly in recent years. Their inert nature means that they can be left *in situ* for



long periods of time and periods up to 4 and even 6 months have been suggested.

Case Report

A 44-year-old woman presented with a 6-month history of backache and intermittent swelling of the left leg. A diagnosis of primary lymphoedema was made and treatment with a support stocking initiated. The swelling persisted 6 weeks later and she had an obvious iliofemoral thrombosis. She was also found to be uraemic. A CT scan showed enlargement of the iliac, para-aortic and mediastinal lymph nodes, and bilaterally obstructed ureters. The lung fields, liver and spleen were normal. Bilateral 5F double-J silicon stents were inserted endoscopically and a laparotomy performed. This showed extensive retroperitoneal tumour, histologically a non-Hodgkin's lymphoma, and chemotherapy with vincristine, cyclophosphamide, doxorubicin and prednisolone was commenced at monthly intervals.

Four months after inserting the stents it was decided to remove them and to repeat the IVU to assess response. However, at cystoscopy, the bladder portions of the stents were densely encased in calcareous material and were very brittle. Luckily the ureteric portions of the stents were removed intact but some encrustation was visible on the portions lying in the kidney (Fig.).

The serum creatinine, calcium, phosphate and the urinary calcium/creatinine ratio were all normal and the urine had been sterile at all times. The IVU showed a return of the obstruction and the stents were replaced. They were left for only 3 months this time but on removal were already encrusted, with the material shown to be pure calcium phosphate similar to whitlockite.

It is suggested that stents should be removed or changed at an early stage in patients with malignancy, especially those having chemotherapy.

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Kaposi's Sarcoma of the Penis

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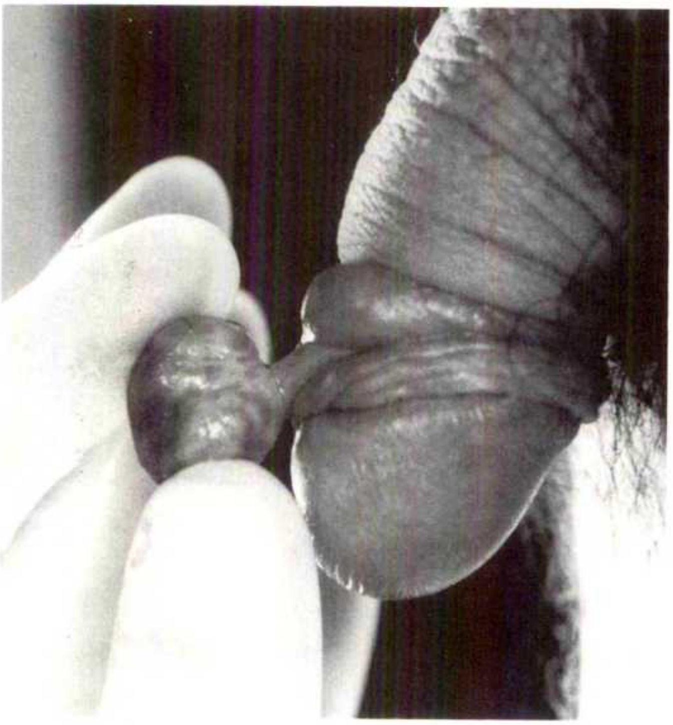
Case Report

D.A., a 47-year-old Italian, was hospitalised following the appearance, 2 months earlier, of a brown pedunculate lesion located lateral to the frenulum on the internal sheet of prepuce (Fig.). The patient denied homosexuality and drug abuse and had received no blood transfusions.

Examination revealed a left inguinal lymphadenopathy. At operation the patient was circumcised, with total excision of the lesion and lymph node biopsy. Histological examination revealed Kaposi's sarcoma. The lymph node was the site of an inflammatory unspecific reaction.



Serological investigations (VDRL, lymphocyte typing, HTLV III and cytomegalovirus titres) and radiology (chest X-ray, CT scan, lymphangiography) were all negative. Ten months post-operatively the patient remains well, with normal serology.

Comment

Kaposi's sarcoma is considered to be a multifocal neoplasm. There is a European form (prevalent in South-East Europe) and an African form. The former usually occurs in patients of middle age or older and is relatively benign; the latter may occur in young people and is more aggressive, with early systemic involvement.

Kaposi's sarcoma confined to the genitalia is extremely rare and only about 20 cases have been reported in the literature (Houston *et al.*, 1975; Conger and Sporer, 1985; Saftel *et al.*, 1986; Merimsky *et al.*, 1987). The present case probably belongs to the classical European form. The possibility that it may be the first clinical manifestation of a systemic disease, and the increasingly frequent association between Kaposi's sarcoma and AIDS, emphasise the need for immunological and radiological studies.

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Renal Cortical Abscess

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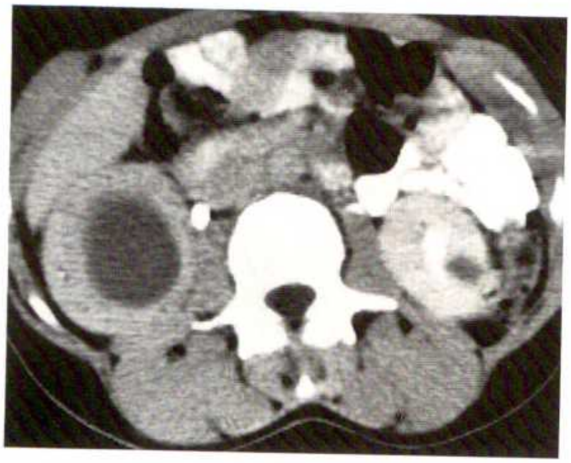
Case Report

A 39-year-old female presented in November 1986 complaining of right upper abdominal pain with malaise, tiredness and anorexia for 6 weeks. She admitted to slight dysuria and intermittent cloudy urine. Abdominal examination was normal. Her urine specimen was found to be frankly turbid and bacteriological examination revealed a pure growth of *Staphylococcus aureus* $> 10^5$/ml. An IVU showed a mass in the lower pole of the right kidney and ultrasound scan suggested that this was a



thick-walled cystic lesion with echoes from within it indicating it was not a simple cyst.

A CT scan (Fig.) showed expansion of the lower half of the right kidney with a central area of low attenuation representing a cavity and a similar small area in the left kidney.

A diagnosis was made of renal cortical abscess which had drained spontaneously into the collecting system. The patient was questioned again regarding her history prior to developing the renal abscess to establish if she had had any distal foci of infection. The only additional information was of a severe bout of psoriasis which had settled under treatment about 6 weeks before becoming symptomatic with the renal abscess. Investigations revealed no occult infective foci in the chest, sinuses or teeth. It was felt that the staphylococci had probably gained access to the body through superadded infection of the psoriatic lesions. As the abscess was draining, and as there was a good initial response to antibiotics, she was continued on cephradine for 6 weeks. CT scan was repeated in 12 weeks and this showed a gradual decrease in the size of the abscess. There was complete resolution by 1 year, leaving only ischaemic areas with some calcification on the right. The patient remains well and symptom-free.

Discussion

Most renal abscesses are now secondary to urinary tract infection caused by gram-negative organisms (Morgan and Nyberg, 1985). Until the 1950s, however, the primary mechanism was by haematogenous spread and the causal organism was *Staphylococcus aureus* (Timmons and Perlmutter, 1976).

As in this case, there is often a prolonged interval between the occurrence of the primary distal infection and the presentation of the renal abscess (Cobb, 1966). Cobb also pointed out that while 95% of reported cases of renal suppuration have been unilateral, the mechanism of haematogenous spread implies that the organisms should have appeared at least evanescently in the opposite kidney. The bilateral abscesses in this case illustrate this point.

A renal abscess may either drain into the collecting system, perforate the renal capsule to form a perinephric abscess, or remain as a chronic intraparenchymal abscess (Morgan and Nyberg, 1985). Conservative treatment of staphylococcal renal abscesses with antibiotics alone has been shown to be successful, but the antibiotics should be continued for at least 4 weeks (Schiff *et al.*, 1977). Conservative treatment has not been satisfactory in the more common gram-negative abscesses and they should be treated by percutaneous drainage and antibiotics (Cronin *et al.*, 1984), reserving open surgical drainage for those cases which do not respond to less invasive treatment.

Acknowledgement

We thank Dr R. N. Setia, Radiologist, Bradford Royal Infirmary.

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Spontaneous Perforation of Squamous Cell Bladder Carcinoma Associated with Hypercalcaemia

R. WUJANTO, R. BROUGH and P. H. O'REILLY,
Department of Urology, Stepping Hill Hospital, Stockport

Case Report

A 79-year-old woman, who had previously been investigated for hypercalcaemia with negative findings, presented as an emergency following sudden onset of lower abdominal pain. On examination she was moribund and grossly dehydrated. There were clinical signs of generalised peritonitis but plain abdominal X-rays showed no evidence of free gas or fluid levels. Blood investigations revealed marked leucocytosis (wcc = 31.7) and uraemia (urea = 21.8 mmol/l; creatinine = 354 μmol/l). Serum amylase was normal. Following resuscitation and intravenous fluid replacement, a laparotomy was performed and 2 litres of purulent, free-peritoneal fluid was drained. The source of the fluid was a perforated bladder the wall of which had been necrosed by primary bladder tumour which extended over the entire bladder surface. A loop of small bowel was adherent near the perforation site with a malignant nodule on the adjacent mesentery. A full thickness biopsy of the bladder wall, and the mesenteric nodule, were sent for histological examination. The defect in the bladder wall was closed with interrupted catgut sutures after the insertion of a urethral catheter. Peritoneal lavage was performed and the abdominal wound closed, draining the pelvic cavity next to the perforation site.

Histology of the bladder wall showed a moderately differentiated primary squamous cell carcinoma; the mesenteric nodule showed metastatic tumour. Postoperative recovery was initially satisfactory with blood urea and creatinine returning to normal levels. However, corrected serum calcium levels were persistently elevated at more than 3.6 mmol/l (normal range 2.20 to 2.55). Serum phosphate, alkaline phosphatase and parathormone levels were all normal. An intravenous urogram and cystogram on the 12th post-operative day showed a non-functioning right kidney and an obstructed left urinary system at the level of the vesicoureteric junction due to tumour infiltration of both lower ureters. The bladder perforation had apparently healed. However, the patient's general condition gradually deteriorated and she died on the 24th post-operative day.

Comment

Squamous cell carcinoma of the bladder accounts for less than 5% of all bladder tumours and is usually associated with chronic inflammatory conditions. The coexistence of hypercalcaemia and primary bladder tumour in the absence of bony metastases is a rare, though recognised, phenomenon (Boissonnas *et al.*, 1982; Bennett *et al.*, 1986). Most of the reported cases have been in association with squamous cell rather than transitional cell carcinoma (Michel *et al.*, 1984). The presentation of such a syndrome by acute spontaneous intraperitoneal bladder perforation has not previously been described.

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Fosfestrol-induced Porphyria Cutanea Tarda

I. H. COULSON and K. MISCH, *Department of Dermatology, Kingston Hospital, Kingston upon Thames*

In 1978 a 69-year-old man with a poorly differentiated prostatic carcinoma was commenced on oral fosfestrol (Honvan) to relieve his symptoms of bladder outlet obstruction. The dose was reduced from 100 mg 4 times a day to a maintenance dose of 100 mg once daily over a period of 7 months and he has remained on this dose since then.

In the summer of 1982 he developed fragility of the skin over the dorsal aspect of both hands and this has recurred during each subsequent summer. Blisters, which ruptured to produce shallow erosions before healing to produce small scars, were noted (Fig.). In recent years, blisters and erosions have developed on the bald scalp. Elevated levels of urinary coproporphyrin and uroporphyrin confirmed the clinical diagnosis of porphyria cutanea tarda (PCT).

For the last 20 years he has enjoyed 1 double whisky every evening, though liver function tests and erythrocyte mean cell volume have remained within normal limits.

Comment

Blisters, erosions, scars, milia and hypertrichosis on the light exposed areas of the skin are the clinical

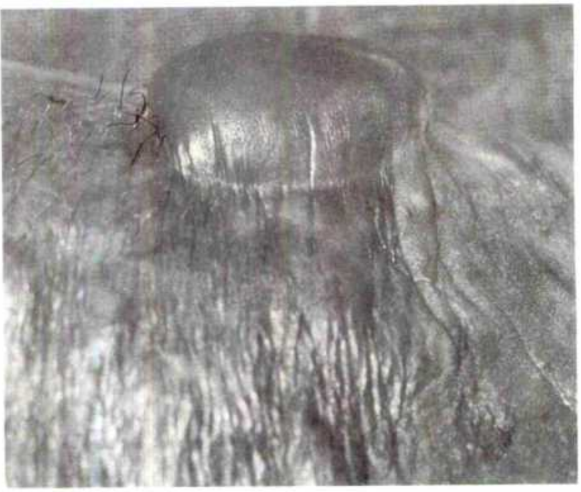

Fig. A large blister on the dorsum of the hand. Atrophic scars remain at sites of previous blisters.

hallmarks of PCT. Its precise pathogenesis is ill understood, though an inherited deficiency of the enzyme uroporphyrinogen decarboxylase (URO D) is documented. Full expression of the disease is thought to be unmasked by ingested toxins, most commonly alcohol. Toxin induction of the hepatic enzyme δ amino-levulinic acid and further suppression of activity of URO D results in increased porphyrin synthesis and this probably produces the elevation of urinary uroporphyrin and coproporphyrin excretion that characterises this disease.

Stilboestrol-induced PCT in men receiving this drug for the treatment of prostatic carcinoma is well reviewed in the dermatological literature (Copeman *et al.*, 1966; Roenigk and Gottlob, 1970), though the urological literature contains only a single case report of this condition (Weimar *et al.*, 1978). Other oestrogens used as oral contraceptives and hormone replacement therapy have been reported to induce PCT in women and there is evidence that they inhibit URO D activity.

This is the first report of PCT occurring in a patient receiving fosfestrol; it is, of course, possible that the regular ingestion of alcohol also contributed to the development of porphyria. It serves to remind us of this rare and distressing complication of oestrogen therapy.

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Adenocarcinoma in a Substitution Caecocystoplasty

C. KADOW, N. D. HEATON, T. PAES, A. J. YATES-BELL and D. A. PACKHAM, *Department of Urology, King's College Hospital, London*

Tumour development is a well recognised complication of urinary diversion into the sigmoid colon. More recently, tumours have been described following augmentation ileocystoplasty (Stone *et al.*, 1987) and a single case of tumour in a defunctioned caecocystoplasty has been reported (Kirby and Lloyd-Davies, 1985). We describe a case of tumour presenting 15 years after substitution caecocystoplasty.

Case Report

A 39-year-old male had a subtotal cystectomy and substitution caecocystoplasty in 1972 for chronic, non-specific granulomatous cystitis which had produced a small shrunken bladder. The following year the lower half of his right ureter became occluded by the same disease process and was replaced with an ileal segment. There was no bacteriological evidence of tuberculosis in either operative specimen. The patient remained well at regular follow-up apart from occasional urinary tract infections. In 1986 he complained of suprapubic pain and intermittent haematuria which did not settle with antibiotic therapy. Cystoscopy revealed a large area of debris and mucus over the trigone area with an underlying tumour mass at the junction of bowel with bladder remnant. Histology showed a poorly differentiated, mucin-secreting adenocarcinoma.

CT scan showed that the tumour mass was confined to the cystoplasty apart from one small area on the left side where it had penetrated into the seminal vesicle (Fig. 1). The patient had a total cystoprostatectomy with removal of the caecocystoplasty. The ileal segment of the right ureter was brought out to the skin surface as an ileal conduit. The operative specimen revealed a large, necrotic tumour occupying the posterior wall of the cystoplasty and arising at the junction of the bowel with bladder remnant (Fig. 2).

Comment

Although colonic cancer is a well recognised complication of ureterosigmoidostomy, it has been stated that the risk of tumours developing in large

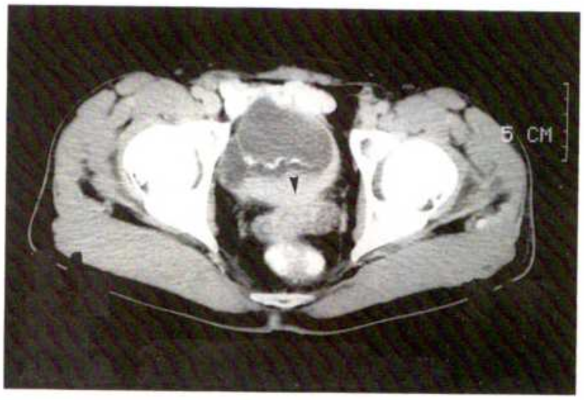

Fig. 1 CT scan of the pelvis showing tumour arising from the bladder and invading the left seminal vesicle (arrowed).

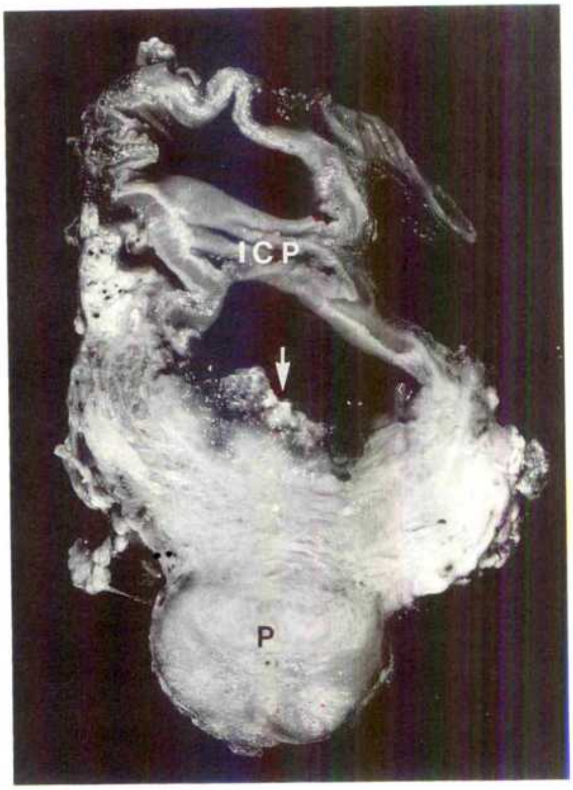

Fig. 2 Operative specimen opened to reveal tumour in the trigone (arrowed), the ileocaecocystoplasty (ICP) and the prostate (P).

bowel reconstructions away from the faecal stream appears negligible (Stone *et al.*, 1987). This is the second case of tumour in a caecocystoplasty and exhibits many features commonly associated with the late complication of ureterocolic diversion. The increasingly widespread use of large bowel segments for bladder reconstruction will, over the next 2 decades, provide further information on the incidence and possible pathogenesis of this sinister complication. Guidelines for the optimal follow-up of patients who have undergone this form of reconstruction will need to be developed.

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Communicating Renal Duplication of Horseshoe Kidney

A. A. MOHSEN and A. F. AZMY, *Departments of Surgery, Cairo University, Egypt, and Royal Hospital for Sick Children, Glasgow*

Communication between the upper and lower moieties of each side and the lower moieties of both sides of a horseshoe kidney in a child is reported.

Case Report

A 13-year-old female with Turner's syndrome presented with abdominal pain and recurrent urinary tract infections. Renal sonar showed dilatation of the upper tract and IVU confirmed the presence of a horseshoe kidney, with a calculus in the right moiety.

Radionuclide DTPA scan with frusemide and bilateral retrograde pyelograms failed to show any hold-up. Laparotomy was performed through an upper transverse incision to remove the calculus. There was bilateral duplication of both moieties with complete duplication of the ureters on the right and dilatation of all pelvicaliceal systems.

There was no obstruction at the pelviureteric junctions but the ureters were inserted high up on the renal pelves. A large calculus in the right upper moiety had eroded through the renal pelvis and caused dense adhesions. The

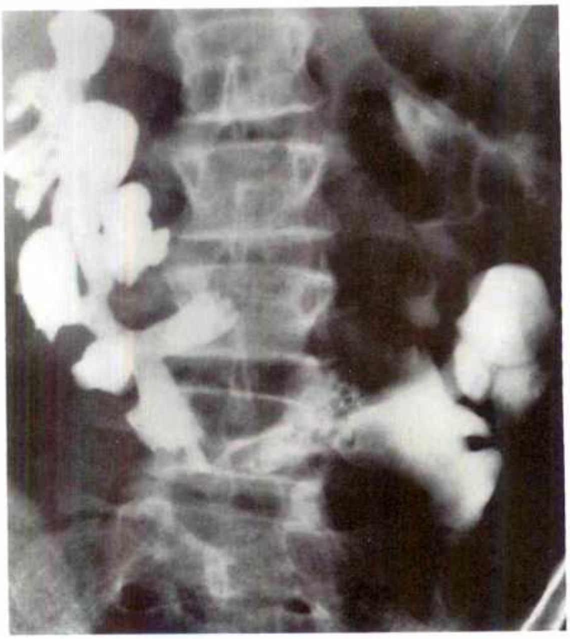

Fig. 1 Nephrostogram through right upper moiety showed filling of all 4 pelvicaliceal systems in the horseshoe kidney.

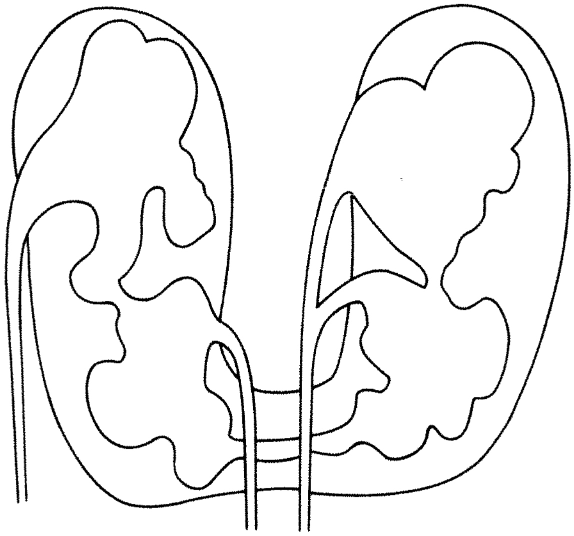

Fig. 2 Diagram illustrates the communication between the duplicated systems.

stone was removed and a nephrostomy tube was inserted. A post-operative antegrade pyelogram through the nephrostomy tube showed a dilated system; the dye then filled the lower moiety on the same side and subsequently filled the lower and upper moiety on the left side (Figs 1 and 2).

Comment

Upper urinary tract duplication of the horseshoe kidney has been mentioned in previous reports (Segura *et al.*, 1972; Wilson and Azmy, 1986) but there has been no emphasis on its surgical implication.

In addition to the fusion anomaly of the lower poles, there is usually failure of rotation of the kidneys; as a result of this the pelves are anterior and often extra-renal. The pelves are usually in tandem but occasionally they may lie side by side and they very rarely communicate.

In cases where there is interdigitation or communication between the calices, extreme care should be taken during separation and repair of the severed calix to avoid urinary fistula formation.

Communication of the pelvicaliceal systems of a duplicated upper urinary tract is extremely rare and may be explained by absorption of the intervening renal tissue during the process of fusion.

••

Acknowledgement

We thank Miss June Lawson for secretarial assistance.

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0007–1331/89/0063–0652/$10.00

Point of Technique

Use of the Cobra Stent for Insertion of a Ureteric Stent

P. PUPPO, *Department of Urology, University of Genoa, Genoa, Italy*

Intrinsic or extrinsic stenosis, obstructing stones or kinking can make it more difficult to insert a ureteric stent. An angiographic cobra catheter can be used to overcome obstacles that cannot be managed by conventional techniques.

The ureteric ostium is catheterised with an angiographic 35″ straight guide wire with a movable core. A cobra catheter is then introduced over the guide wire along the ureter up to the site of obstruction or kinking. By twisting the curved tip of the catheter the guide is tentatively directed beyond the obstacle (Fig. 1). Once the guide wire has passed the obstacle the cobra catheter is pushed over the guide wire up to the intrarenal collecting system. One of the lower calices is then catheterised (Fig. 2) and the soft movable guide wire is advanced into the calix and stiffened, taking care to avoid perforation. The cobra catheter is withdrawn and the double-J stent inserted over the guide wire.

Comment

The problems of stent insertion can be overcome in most cases by using angiographic techniques. The use of a cobra catheter, originally created for femoral-visceral angiography, is particularly suitable for bypassing ureteric obstructing stones because of the facility offered by the curved tip of leaning the soft guide wire against the ureteric wall and driving it alongside the stone. In the case of ureteric kinking the curved tip can follow the curve

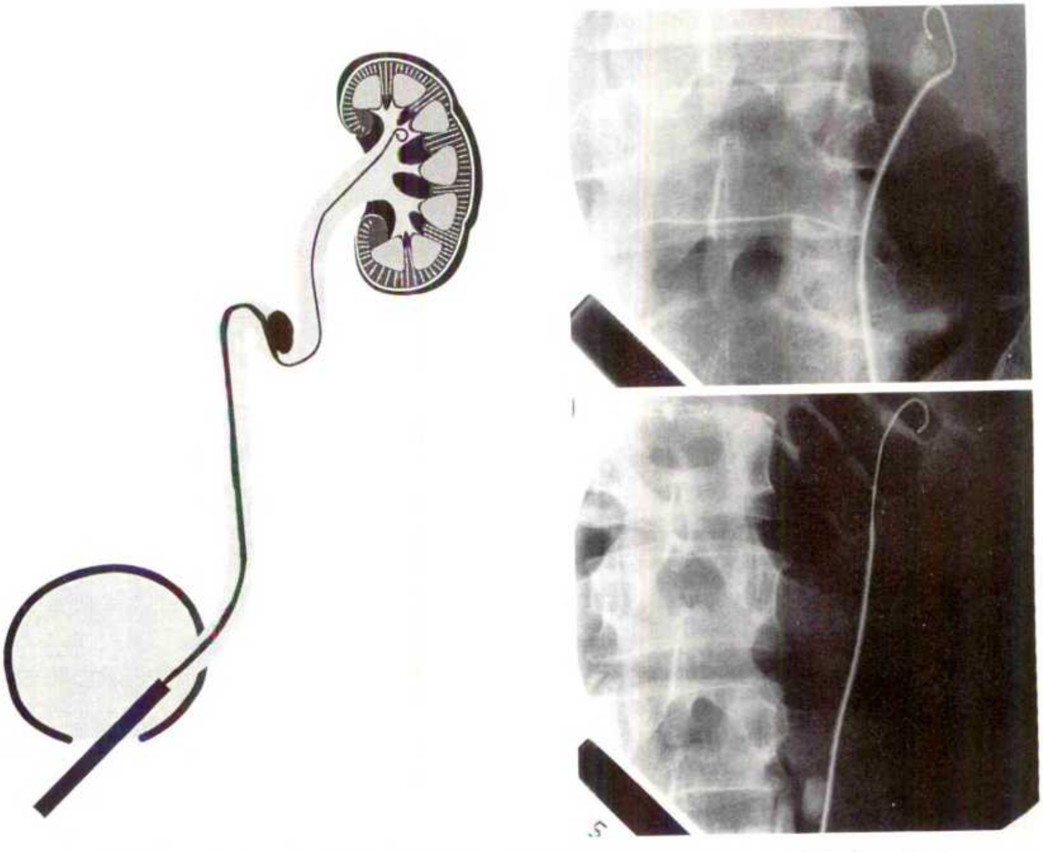

Fig. 1 The curved tip of the cobra catheter leans the soft guide against the ureteric wall and guides it alongside the stone and then up to the pelvis.

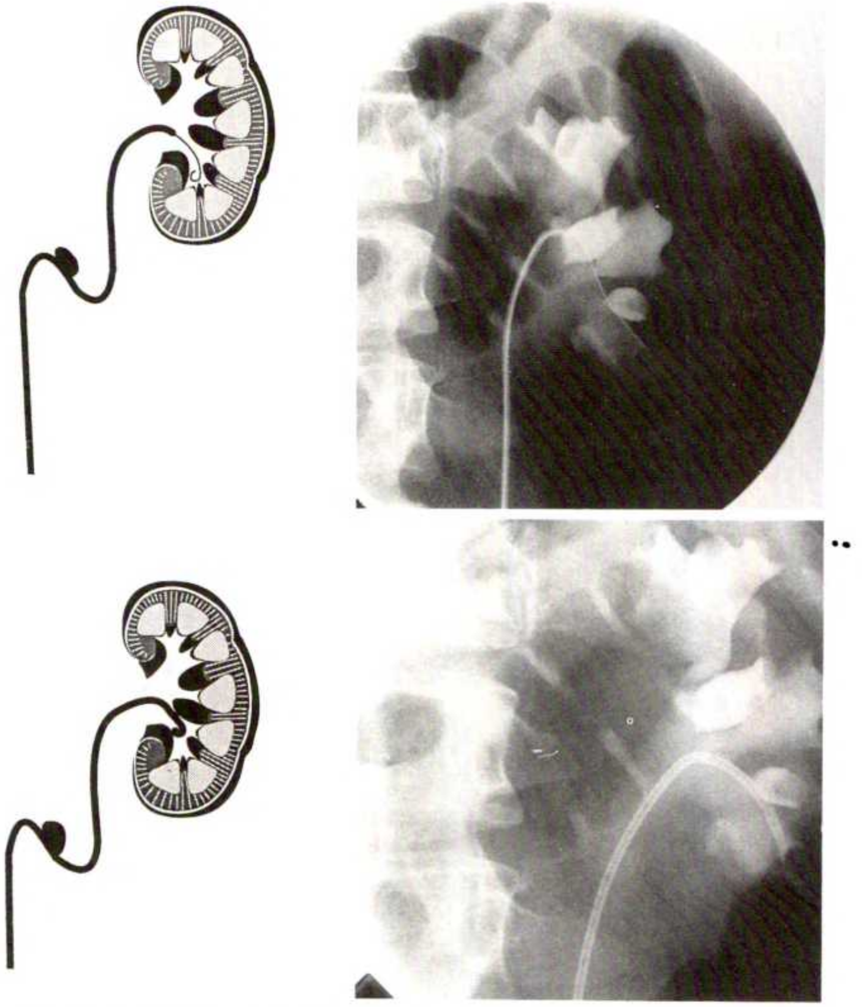

Fig. 2 The cobra catheter permits catheterisation of the selected calix, placement of the guide wire and guidance of the double-J stent into the chosen calix.

of the ureter and allow the soft guide wire to pass up. In most cases the passage of the guide followed by the catheter is sufficient to straighten the ureter in such a way that subsequent manoeuvres are much easier. The shape of the cobra catheter also allows one to choose the calix for the best placement of the stent, so reducing the risk of downward migration. This is useful when the stone fills only a caliceal group which can be entered by the stent, so avoiding obstruction of the caliceal neck. The various steps of the technique may be simplified if a set is used which includes 2 ureteric catheters (1 straight and 1 cobra-shaped), an indwelling stent and a 200-cm guide wire that is compatible with all 3 catheters. The guide has a movable core, so that it can be stiffened or softened according to the circumstances.

Finally, the use of this technique in routine stent placement offers the following advantages.

1) Ability to pass the obstacle in more than 60% of cases where a straight stent with the movable guide has failed.
2) Choice of the calix in which to leave the stent.

The additional cost of this set is low and should not hinder its adoption.

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0007-1331/89/0063-0654/$10.00

Correspondence

Dear Sir,

re **Penile gangrene: a separate entity from Founier's syndrome?** M. Frydenberg. *Br. J. Urol.*, **61**, 532–533, 1988

We read with interest the above Case Report. We have reported a similar type of necrosis that we observed in patients with not only diabetes mellitus but also end-stage renal disease (Bour, J. and Steinhardt, G. *J. Urol.*, **132**, 560–562, 1984). We too found no infective cause for the necrosis and histologically had evidence of both large and small vessel disease in the penectomy specimens. In patients with diabetes and renal failure, the process is particularly malignant and the necrosis is extensive enough to preclude adequate voiding. As reported, we found this lesion to be particularly malignant and both patients died within a short period of developing the penile necrosis.

Yours sincerely,

J. Bour and G. Steinhardt
Pediatric Urology, Cardinal Glennon's Children's Hospital, 1465 South Grand Boulevard, Saint Louis, Missouri 63104, USA.

Reply by M. Frydenberg. I would like to thank Drs Bour and Steinhardt for their comments regarding penile gangrene of a non-infective cause. I can only add support to the fact that the process is an aggressive one, since our patient also died in the post-operative period. Perhaps this is an entity that needs to be recognised early and aggressive surgical treatment undertaken in order to achieve better long-term results.

Dear Sir,

re **Idiopathic retroperitoneal fibrosis. A retrospective analysis of 60 cases.** L. R. I. Baker *et al. Br. J. Urol.*, **60**, 497–503, 1987.

It is surprising that none of the patients with retroperitoneal fibrosis reported by Dr Baker *et al.* presented with anuria. The incidence of anuria has been reported to be 2.5 to 10% in various series (W. Skerr *et al. J. Urol.*, **99**, 575–584, 1968; H. Lepor and P. C. Walsh. *J. Urol.*, **122**, 1–6, 1979; R. C. Tiptaft *et al. Br. J. Urol.*, **54**, 620–624, 1982).

Recently we had a 45-year-old female patient who presented with anuria; her serum creatinine was 14.8% and the kidneys were not visualised on IVU. Pre-operative nephrostomy was performed, following which renal function became normal. The fibrous plaque encasing the right lower ureter was excised and right ureteric reimplantation performed. Three months after presentation a left nephrostomy was inserted and drained 1 litre of urine daily. This was followed by left ureteric reimplantation and omental wrapping of the ureter.

Although ureterolysis of a kidney shown to be "non-functioning" by high dose urography is generally not advisable, we conclude that it can be successful and may be worthwhile in 25% of patients, as Baker *et al.* have shown.

The authors' nomenclature of "unilateral obstruction with contralateral non-function" does not read well. We suggest "bilateral obstruction with one non-functioning kidney", for the non-functioning kidney is, indeed, obstructed.

Surprisingly, the authors mention no difficulty in separating the ureter from the fibrous plaque. A dissection plane between the ureter and the plaque was found in all cases. In addition, there is no mention of the ease of ureteric catheterisation in the obstructed ureters. Invasion of the ureteric wall by fibrous tissue is well known and failure to pass a retrograde ureteric catheter, with the absence of a plane of dissection between the plaque and the ureter is associated with recurrent obstruction of the ureter (G. Cooksey *et al. Br. J. Urol.*, **54**, 628–631, 1982).

Yours sincerely,

S. Khanna
Department of Urology, PGIMER, Chandigarh, India

Reply by L.R.I. Baker et al. We agree with Dr Khanna that idiopathic retroperitoneal fibrosis (periaortitis) may present with anuria. One of our 60 patients presented in this way. As can be seen in Table 1 of our paper, in which main presenting symptoms are listed, 6 patients (10%) were oliguric at presentation.

We did not state that ureterolysis of a kidney shown by technically satisfactory excretion urography and isotopic methods to be non-functioning is *invariably* contraindicated. Our observation that ureterolysis followed by steroid therapy restored only a modest amount of function to 2 of 8 such kidneys, whilst 6 remained non-functioning, leads us to the view that operating upon such kidneys is usually unrewarding and inadvisable.

We used the term "unilateral obstruction with contralateral non-function" since this is strictly accurate. We agree that the vast majority of non-functioning kidneys in patients with idiopathic retroperitoneal fibrosis have been damaged by long-standing obstruction; however, other causes of non-function do exist.

Ureteric catheterisation – which is typically easily achieved – is nowadays much less often carried out in such patients. If relief of obstruction is required before operation, antegrade percutaneous nephrostomy is more comfortable for the patient and is associated with less risk of infection.

We accept that the ease with which the fibrotic tissue can be separated from the ureter varies from patient to patient and that, on occasion, it may be difficult to find a plane of dissection. One of our patients (Table 3 of our paper) developed a urinary leak following ureterolysis which was a contributory cause of death. In general, however, separation of the ureter from fibrotic tissue was achieved uneventfully.

Dear Sir,

re **Benefits of combination therapy with flutamide in patients relapsing after castration.** F. Labrie *et al.* *Br. J. Urol.*, **61**, 341–346, 1988.

Labrie *et al.*, in their report of an uncontrolled study of Flutamide in patients following relapse to primary hormonal therapy, conclude that "flutamide in association with castration (surgical or medical) is the drug of choice for patients who relapse after castration or treatment with an oestrogen or an LHRH agonist alone." I do not believe this conclusion is defensible.

The only possible evidence in the paper that could support this conclusion is in Figure 2, which compares the survival of their patients with those in a report from a National Prostatic Cancer Project. The remaining figures and data presented with respect to the other endpoints (response, survival by response) are not relevant to their main conclusion since no concurrent or historical control data forming a basis for comparison are provided. Also, as is discussed below, it is invalid to use response-specific survival to conclude efficacy.

The survival for the NPCP patients in Figure 2 does not differ substantially from other reports of survival for patients failing hormonal therapy. From the Figure one can extract that the median survival from the NPCP data is approximately 7 months compared with approximately 12 months for the Labrie *et al.* patients (or, as they reported, the 2-year survival rates are 16 and 38% respectively). This would seem to be a large difference but no data are presented which justify the comparison. For example, are the NPCP patients comparable to the patients reported by Labrie *et al.* with respect to performance status, age and sites of metastasis? I argue that the patients used in the Labrie study had less severe disease than NPCP patients enrolled in studies of advanced prostate carcinoma.

Table 1 of the article by Labrie *et al.* states that 36.4% of the patients had loss of body weight but the NPCP reports 52.7% with weight loss. Similarly, Labrie *et al.* report only 0.9% of patients with urinary obstruction compared with 29% of the NPCP patients. Among the Labrie patients, 22.0% are reported to have been bedridden some part of the time compared with 29.4% of the NPCP patients. In the opposite direction, 79.0% of the Labrie patients are reported to have some pain compared with 71.7% of the NPCP patients. These comparisons are subject to a variety of limitations but the weight of evidence indicates that patients enrolled to NPCP protocols for advanced prostate cancer (which include 31% newly diagnosed) had more severe disease than the patients used in the Labrie study.

Table 2 of the Labrie paper shows the number of patients with metastases at various sites. From this one can infer that a minimum of 87.4% and a maximum of 89.5% of the patients they studied had bone as the only site of metastasis. Unfortunately, the NPCP data do not include the proportion of patients who had bone as the only site of metastasis but it is reported that 5.4% of patients did not have bone metastasis. D.F. Paulson *et al.* (*J. Natl. Cancer Inst.*, **63**, 615–622, 1979) reported that 67% of patients in their study had bone metastasis only and the overall survival of their patients is comparable to the survival rate in other studies of hormonally unresponsive patients.

The reader of the Labrie paper is asked to accept the primary conclusion based on the Kaplan-Meier plot comparing the survival data from two diverse sources, the NPCP and the Laval University Medical Center. There are two extremes of interpretation: either the patient groups are comparable and the survival difference is real, or the survival difference is due only to the better prognosis of patients studied by Labrie. I have argued that the latter explanation is feasible. Labrie *et al.* readily accept the former. Unfortunately, the data to resolve this difference in interpretation do not exist, for Labrie *et al.* chose to perform their study without a concurrent and randomly chosen control group, or even a retrospective control group from their own institution.

I have two other criticisms of the paper by Labrie *et al.* They report 2 plots of survival with patients classified by response (Figs 3 and 4) and apparently believe that the data presented in these plots provide a justification for their conclusion. The practice of using Kaplan-Meier plots of survival with patients classified by response is common in the reporting of results from cancer studies, but it is not a valid method of concluding efficacy of a treatment (J.R.' Anderson *et al. J. Clin. Oncol.*, **1**, 710–719, 1983). Finally, the authors state that the response rates reported for their patients illustrate "the influence of the treatment on their quality of life." This statement is not justified by any data presented in the paper. The assessment of the impact of a treatment on the quality of life requires explicit methodology for the assessment of the quality of life. This methodology was apparently not a part of their study.

Yours sincerely,

B. A. Blumenstein
Southwest Oncology Group – Statistical Center,
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Columbia Street, Seattle, Washington 98104, USA.

Reply by F. Labrie. Although the term is cherished by some, it seems somewhat arrogant to refer automatically to a non-randomised study as an "uncontrolled study". It should be recognised that a non-randomised study can be very rigorously controlled and, moreover, randomisation by itself is not equivalent to a well controlled study. I would suggest that some statisticians be more discriminatory in the use of terminology and to respect well controlled non-randomised studies such as our own and those of other highly respected scientists.

It is not the purpose of this reply to reactivate the debate between randomised clinical trials and historical controls. In this particular study, where all patients had progression of their cancer despite medical or surgical castration, it seems that using patients as their own controls is fair. We doubt that a randomised clinical trial would have provided more information, for we estimate that the arrest of disease progression as evaluated by the NPCP criteria was a clear indicator of the efficacy of the drug. A randomised clinical trial would have required a controlled group receiving placebo, an alternative which appears to us and many others to be unethical. We believe that the use of patients as their own controls was the best experimental approach. We would also refer to M.C. Weinstein (*N. Engl. J. Med.*, **291**, 1278–1285, 1974) and S. Hellman (*Cancer Clin. Trials*, **2**, 189–193, 1979), who indicated that randomised clinical trials do not have the ultimate properties apparently seen by Dr Blumenstein.

In addition to his unjustified biased prejudice, Dr Blumenstein should have understood the basic facts about prostate cancer described in our manuscript:

1. All patients were in progression at the start of treatment. Thus the 72 responses observed are direct evidence of the efficacy of treatment, which is much more important than Figure 2. Arrest of progressive disease, in our opinion, is the best evidence of efficacy. Those involved in the treatment of this category of patients know that spontaneous remission does not occur at the rate of 34.5%.

2. Concerning Figure 2, one can argue at length about historical controls. However, as stated by Dr Blumenstein himself, the NPCP data do "not differ substantially from other reports of survival for patients failing hormonal therapy". This fact was clearly indicated in our manuscript. Why then argue about the weakness of historical controls when all available "historical" data are superimposable? Instead, I would suggest that the data already published by many groups have merit and are correct. Why should one ignore the results of all previous studies? In any case, comparison of these curves is of negligible importance compared with the arrest of progression observed upon administration of the combination therapy.

3. Dr Blumenstein then argues that "the patients used in the Labrie study had less severe disease than NPCP patients". Our main point is not comparison with the NPCP or other data but the arrest of disease progression at the time of starting therapy. All of the subsequent discussion comparing severity of disease is irrelevant. The discussant should have known that introducing 31% of newly diagnosed patients destroys his argument since these patients have a much better prognosis. Moreover, we did not make any comparison with the group discussed by Dr Blumenstein.

4. The discussion about other sites of metastasis is of no importance; when bone metastases are present, there are also metastases elsewhere. For practical reasons, all studies simply indicate the other easily detectable sites of metastases (especially the lungs). One is not justified in performing a whole body CAT scan, bone biopsy and other elaborate tests in order to detect other sites when bone metastases are already clearly demonstrated and are the predominant findings. Such knowledge of other possible asymptomatic metastases has no influence on the choice of therapy and would only cause inconvenience to the patient and lead to unjustifiable costs.

5. Contrary to the discussant's suggestion, it is useful to correlate survival or duration of response with the type of best response, since such classification can clearly serve as a useful prognostic factor.

When Dr Blumenstein declares the invalidity of using survival time by tumour response while referring to J.R. Anderson *et al.* (*J. Clin. Oncol.*, 1, 710–719, 1983), we would have expected him to read that paper with more attention. On page 713, when describing the landmark method, these authors wrote: "a second valid method for evaluating survival by tumor response selects some fixed time after the initiation of therapy as a landmark for conducting analysis". At a second reading of our paper, he will find that responders and non-responders were determined after the first evaluation at 3 months, which is the landmark used in our study. Statistical methods are an essential part of clinical research but the choice of the proper parameters is at least as important.

It is surprising and deceiving to note that Dr Blumenstein does not realise that obtaining a positive objective response with decreased pain, relief of urinary obstruction and/or hydronephrosis is equivalent to an improved quality of life. What else can more convincingly illustrate quality of life?

If he is not convinced by such large scale and rigidly controlled studies, I would suggest that Dr Blumenstein perform himself a randomised study in a similar group of patients before making any comments and avoid using arguments based on so many misunderstandings of the field of prostate cancer. Before doing so, it would certainly help to read some of the references indicated at the end of our manuscript as well as the vast amount of other available data in the literature indicating that almost superimposable results have repeatedly been obtained using other approaches (surgical and medical) which block adrenal androgens in patients relapsing after standard endocrine therapy. The present data are no surprise to someone aware of the data already published in this area. Flutamide is simply an alternative which is well tolerated, easy to administer and at least as efficient as any other therapy so far available to patients progressing after medical or surgical castration.

(This correspondence is now closed. Ed.)

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Notices

British Association of Urological Surgeons

President: R. T. Turner-Warwick, DSc, DM, MCh, FRCP, FRCS, FACS

Annual Meeting: St Helier, Jersey, Channel Islands. 20–23 June 1989

All correspondence to: Hugh N. Whitfield, MChir, FRCS, Honorary Secretary, British Association of Urological Surgeons, Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN.

BAUS Travelling Fellowship

The British Association of Urological Surgeons offers a Travelling Fellowship of £1000.00 for any article(s) of outstanding merit published each year (2 volumes) in the British Journal of Urology. Candidates for the prize must be Fellows of the Royal College of Surgeons in the British Isles, Canada, Australia or South Africa; they must be undergoing urological training or have obtained a consultant post not more than 10 years before the date of submission of the paper. In the case of multiple authorships the authors would have to decide which of them should receive the prize. The successful prize winner must submit a programme of visits to urological centres outside Britain for consideration by the adjudicators, who shall be the President, the Editor of the British Journal of Urology and the Honorary Editorial Secretary. This prize is not necessarily awarded annually.

C.-E. Alken Prize

An endowment fund has been established to further clinical work and research in the field of Urology by presenting an annual award of SwF 10,000 for outstanding scientific endeavours. The award will be for an unpublished work in the field of Urology. An award certificate will also be presented. The prize money may be divided among several contributors.

The papers may be written in either German or English and three copies must be submitted by 30 September 1989 to: Stiftungsrat C.-E. Alken-Stiftung, Advokaturbüro Dr F. Kellerhals, Bundesplatz 4, CH-3011 Bern, Switzerland.

Each submission must be affixed with a code word and must not bear the author's name. In addition, a sealed envelope labelled with the code word is to be included, containing on a separate sheet of paper the author's name and professional standing, together with the code word.

The adjudicators for the award will be the Board of Directors of the endowment fund and their decision will be final.

Norwich Eaton Travelling Scholarship

The scholarship(s) will cover travel, accommodation and registration expenses associated with attending the Society of University Urological Residents and American Urological Association meetings. They will be awarded annually until such time as either the Senior Urological Registrars Group or Norwich Eaton Ltd decide not to continue and will be available to any person appointed to an accredited urological training post.

The scholarship(s) will be awarded to the person(s) presenting the winning paper at the Senior Urological Registrars Group Annual Meeting. The winning paper(s) will be selected by those members of the Senior Urological Registrars Group present at the meeting and appointed to urological training posts.

Shackman Travelling Fellowship 1990

Applications are invited from Medical Practitioners registered in the United Kingdom who are Senior Registrars in an accredited training programme in urology or Consultant Urological Surgeons of no more than 5 years' duration. Applicants of equivalent university status will also be considered.

The Fellowships are intended to provide sufficient support to enable the holder to undertake a period of study, either in the United Kingdom or abroad, for a period of not less than 6 weeks.

The subject to be studied must be related either to urology or to renal transplantation and may be either a laboratory or a clinical investigation.

The closing date for applications is 1 September 1989.

Further particulars from and all correspondence to: Taylors, Solicitors, 119 High Street, Newmarket CB8 9AG.

Hans Marberger Prize

The Hans Marberger Prize will be awarded for the first time at the meeting of the German Urological Association in Hamburg in 1990. The prize, which will be donated by Karl Storz Ltd, will amount to öS 50,000 and will be awarded biennially for the best paper in the field of reconstructive surgery in urology or endourology. The award may be split.

Papers may be written in either German or English and should be submitted in triplicate to Dr H. Fuchshuber, Adamgasse 15, A-6020 Innsbruck, by 1 March 1990.

A code word should be affixed to each manuscript, which should not bear the author's name. In a separate envelope bearing the code word the following information should be given: author's first name, surname, position, and code word.

Edinburgh Urological Festival

A Joint Postgraduate Urological Meeting: Edinburgh University Department of Surgery (WGH) and Department of Urology, University of California, Davis

Edinburgh. 23–26 August 1989

The programme will consist of review lectures by invited speakers from the USA and Europe, with short papers by participants on the following topics: Superficial Bladder Cancer; Bladder Dysfunction; Reconstructive Surgery; Infertility and Sexual Dysfunction; Neo-adjuvant Chemotherapy; Flow Cytometry in Urology.

Further particulars from: Urological Festival Secretary, University Department of Surgery (WGH), Western General Hospital, Crewe Road, Edinburgh EH4 2XU, UK *or* Professor A. Stone, Department of Urology, University of California, Davis, Sacramento, USA.

Annual Meeting of the Swiss Society of Urology

Aarau, Switzerland. 21–23 September 1989

The main themes will be Renal Carcinoma and Ultrasound in Urology.

Further information from: Professor R. Tscholl, Urologische Klinik, Kantonsspital, CH-5001 Aarau, Switzerland, or Professor D. Hauri, Urologische Klinik, Universitätsspital, CH-8091 Zürich, Switzerland.

Fourth Steglitz Pediatric Surgical Symposium: Laser Application in Children

Berlin, West Germany. 10 and 11 November 1989

Further information from: Dr Felix Schier, Department of Pediatric Surgery, Free University of Berlin, Hindenburgdamm 30, 1000 Berlin 45, West Germany.

Archivos Españoles de Urologia

Readers are advised that the above journal now has a new publisher. To ensure that subscribers continue to receive their copies of the journal they are requested to contact Ediciones BOK, S.A., Pilar Millan Astray, 4, esc. 2, 1.°A, 28009 Madrid, Spain.

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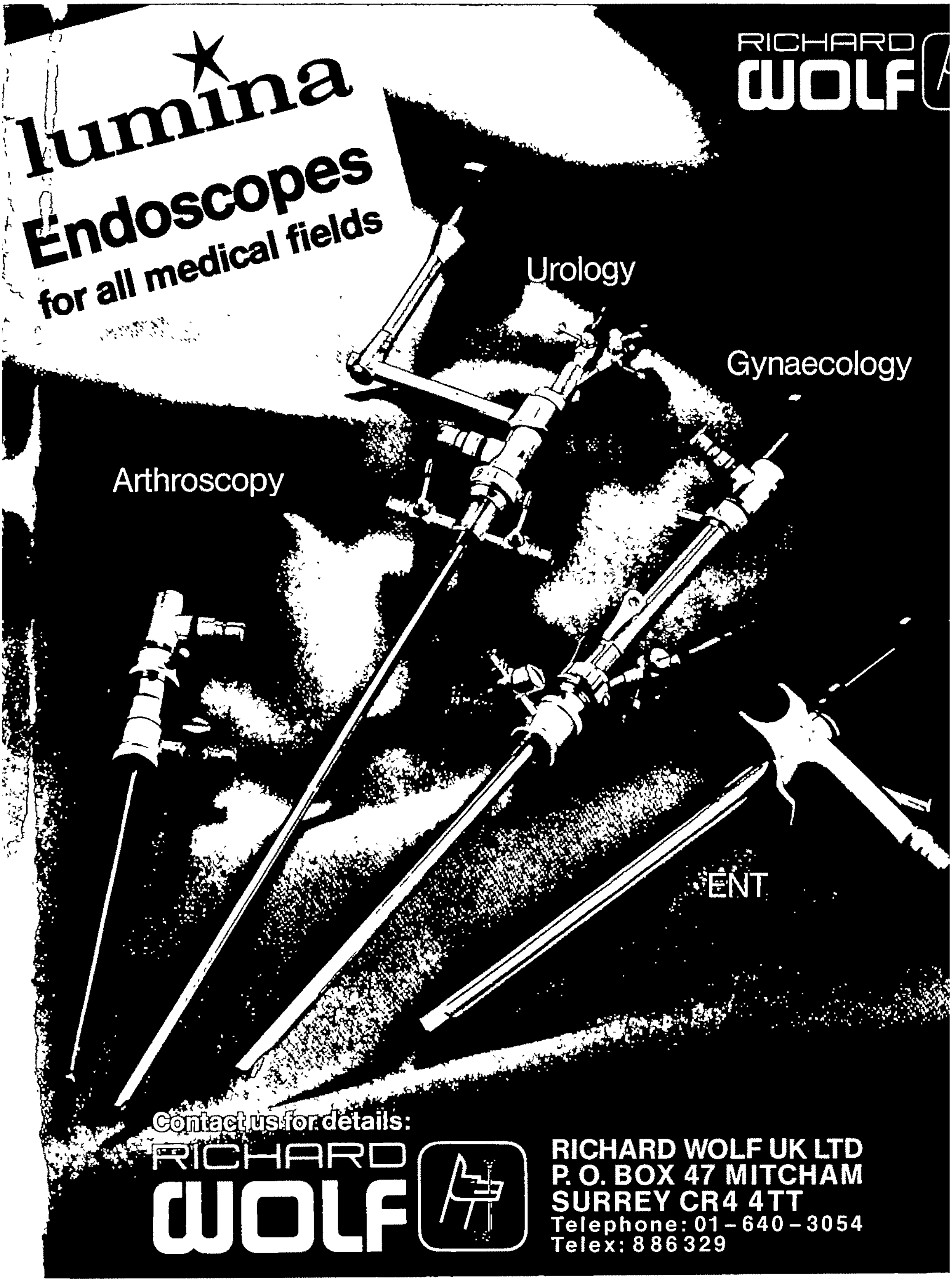

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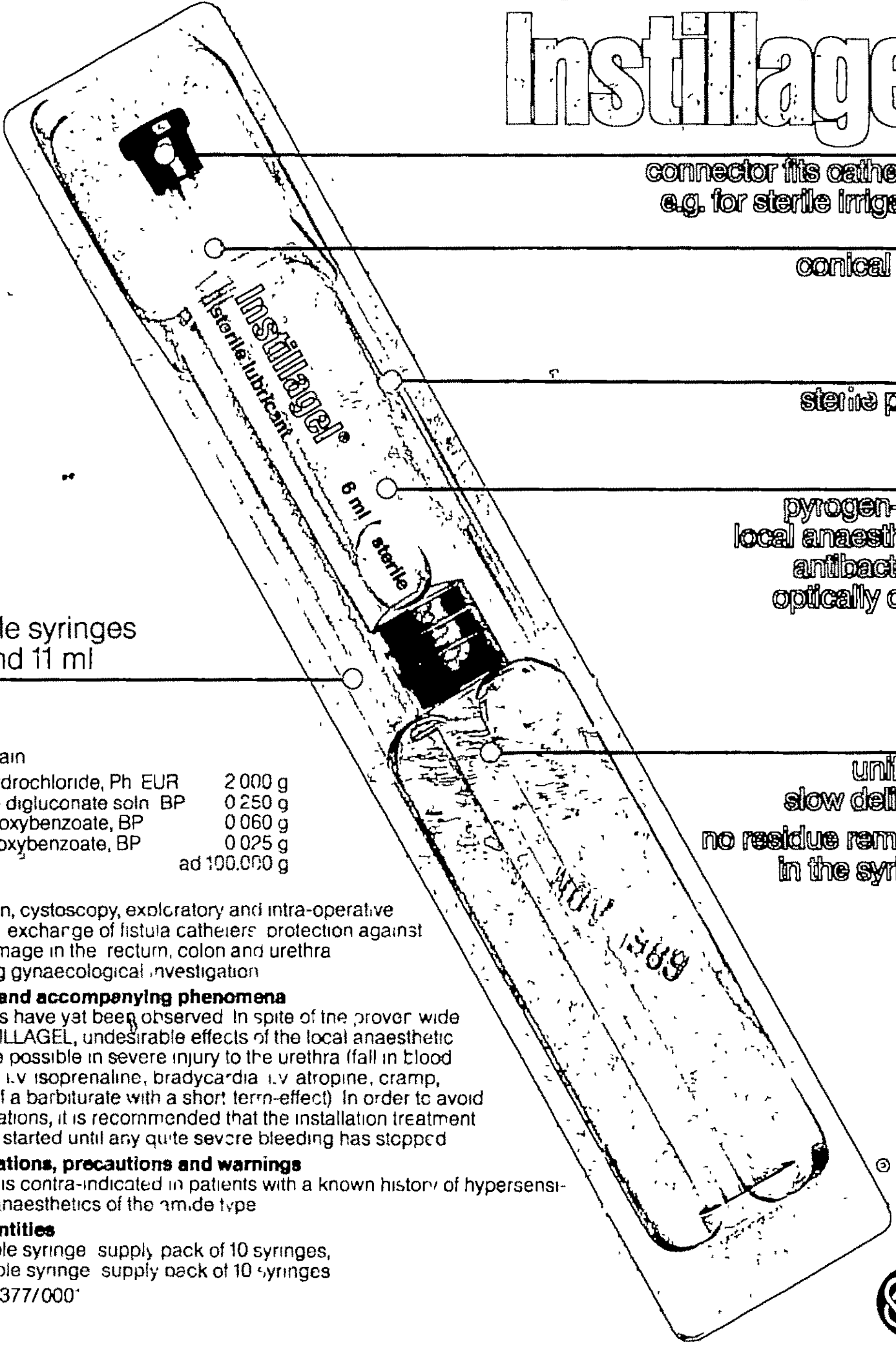

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